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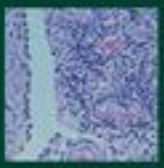

Fibromyalgia Syndrome

SECOND EDITION · SECOND EDITION · 2

ERNEST CHOY

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Second edition

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To Christina, Catrina, and Nicholas,
for all their support and forbearance

Preface to the second edition

Since the first edition of this book, fibromyalgia syndrome has become increasingly recognized and diagnosed. Unfortunately, there is still a significant delay in patients getting a diagnosis. Many countries have recognized the healthcare burden of fibromyalgia and have published guidelines and recommendations on diagnosis and management. The Canadian guidelines emphasized that the diagnosis could be made in primary care and the importance of empowering patients to manage this chronic illness. To assist this, there are new diagnostic criteria that could be applied in primary care to aid recognition and diagnosis.

Professor Ernest Choy, 2015

Preface to the first edition

Fibromyalgia syndrome is characterized by chronic widespread pain. It is common, affecting 2% of the population. The prevalence has increased dramatically since 1990. The condition is not new but has been known by various names such as fibrositis or myofascial pain syndrome, until 1990 when the American College of Rheumatology (ACR) published new classification criteria and first used the term fibromyalgia. The absence of an objective diagnostic test and overlap with other conditions often lead to significant delay in diagnosis. There is a general concern by medical professionals that fibromyalgia is an ill-defined, polysymptomatic condition. The diagnosis of fibromyalgia may create an illness and increase greatly healthcare cost. However, research has found evidence of the opposite. The diagnosis of fibromyalgia improved patient satisfaction and reduced healthcare utilization through decreased referral to other specialists and medical investigations. Hence, prompt diagnosis is beneficial to patients, doctors, and healthcare providers.

The purpose of this short book is to provide a succinct and practical guide to help general practitioners and rheumatologists to diagnose and manage patients with fibromyalgia. This book will provide the reader with an essential understanding of the pathophysiology of pain in fibromyalgia, different subtypes of fibromyalgia, and pitfalls in the diagnosis and management of this chronic condition.

Professor Ernest Choy, 2009

Contents

Abbreviations

ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
APS	American Pain Society
BDI	Beck Depression Inventory
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
cm	centimetre
CNS	central nervous system
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSQ	Coping Strategies Questionnaire
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
FIQ	Fibromyalgia Impact Questionnaire
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
FMS	fibromyalgia syndrome
FS	Fibromyalgia Symptom (scale)
GABA	gamma-aminobutyric acid
HADS	Hospital Anxiety Depression Scale
HAQ	Health Assessment Questionnaire
HPA	hypothalamic–pituitary–adrenal axis
HRT	hormone replacement therapy
kg	kilogram
mg	milligram
MINI	Mini International Neuropsychiatric Interview
mm	millimetre
MRI	magnetic resonance imaging
NGF	nerve growth factor
NMDA	N-methyl-d-aspartate

NSAID	non-steroidal anti-inflammatory drug
PET	positron emission tomography
rACC	rostral anterior cingulate cortex
REM	rapid eye movement
RF	rheumatoid factor
SF-36	Short Form-36
SNRI	serotonin and noradrenaline reuptake inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SSS	Symptom Severity Scale
STAI	State-Trait Anxiety Inventory
VAS	visual analogue scale
VIP	vasoactive intestinal peptide
WPI	Widespread Pain Index

Chapter 1

How to diagnose fibromyalgia syndrome

Key points

- Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain.
- Fatigue, unrefreshed sleep, depression, stiffness, anxiety, and problems with cognition are common associated symptoms.
- Physical disability due to pain is common.
- American College of Rheumatology (ACR) criteria for FMS stipulates the presence of chronic widespread pain defined as pain in all four quadrants of the body, as well as in the axial skeleton, for at least 3 months on a more or less continuous basis.
- 'Red flag' symptoms include unexplained weight changes and fever.
- 'Red flag' signs are joint swelling, muscle weakness, abnormal gait, skin rashes, delayed tendon reflexes, and lymphadenopathies.

1.1 Introduction

Fibromyalgia syndrome (FMS) is not a new medical condition, although the term has only been used since 1990 when the American College of Rheumatology (ACR) classification criteria were published. Numerous names, including muscular rheumatism, myalgia, interstitial fibrositis, myofascitis, and myofascial pain, had been used to describe this condition prior to 1990. Although the term 'fibromyalgia syndrome' may not be ideal, it does not imply causation and describes the commonest symptom—chronic widespread pain. For the present, 'fibromyalgia syndrome' seems an appropriate compromise.

1.2 Clinical features: symptoms and signs

1.2.1 Pain

The universal feature in FMS is chronic widespread pain. This is defined as pain affecting both sides of the body, as well as above and below the waist, lasting for more than 3 months. Pain is predominantly diffuse, but some regions may be more painful at different times. Characteristically, the patient complains 'I hurt all over all the time'. In some patients with FMS, there is a history of chronic local pain, such as low back pain, before developing more widespread symptoms.

Pain is variably described as burning, aching, or soreness. Although pain is present throughout the day without any significant diurnal variation, the location may change, and the intensity varies. Physical activity often makes pain worse. However, many patients also complain of

spontaneous pain without any obvious precipitating factor. Pain is often described as a chronic ache with occasional sharp spasm. Some patients describe their muscles to be tense and 'tied in knots'. Often patients complain of severe pain, which is disabling. They cannot manage routine household chores, especially shopping and cleaning. Those patients who are in employment often find it difficult coping with work. Simple analgesics, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), are rarely effective.

One of the characteristic features of FMS is 'tenderness'. Patients often complain that even light touch or pressure is painful. Some patients complain that the slightest touch can make them recoil in pain.

Other painful conditions, such as headache, migraine, non-cardiac chest pain, heartburn, dysmenorrhoea, and irritable bowel syndrome, are common in patients with FMS.

1.2.2 **Other major symptoms**

Aside from pain, fatigue, non-restorative sleep, stiffness, depression/anxiety, dyscognition, and disabilities are common in patients with FMS.

1.2.2.1 *Fatigue*

Fatigue is common in patients with FMS. Many patients rank fatigue as the second most disabling symptom. It is often worse in the morning and early evening. Some patients associate fatigue with mild physical or mental exercise. Whilst the severity of fatigue varies, in general, it is less disabling than chronic fatigue syndrome. Nevertheless, in some patients, fatigue reduces their ability to perform daily chores and negatively impacts their quality of life.

1.2.2.2 *Non-restorative sleep*

Non-restorative sleep affects many patients with FMS. It is of pathogenic importance in some patients with fibromyalgia (FM). This will be explained in more detail in Chapter 2. Patients often do not complain of sleeping disorder spontaneously. On enquiry, poor sleep quality occurs in about 65% of patients. Patients often report not feeling refreshed after a full night's sleep, resulting in patients feeling tired, drained, and physically incapable of dealing with daily tasks. Many FM sufferers find that they just cannot get adequate rest. Many feel drained and sleepy during the day and want to get back to sleep in the morning. In some cases, patients complain of waking several times at night. Some patients link sleep disturbance to the level of pain or fatigue. Interestingly, insomnia/difficulty in falling asleep is less common. Sleep disturbance is particularly common in patients who suffer from frank sleep apnoea. In patients who complain of loud snoring and disturbances of breathing during the night, co-morbid primary sleep disorders, such as obstructive sleep apnoea syndrome, should be suspected.

Restless leg syndrome occurs in 20–40% of patients with FMS, with unpleasant sensations in the lower limbs occurring at night, so much so that the limbs have to be moved in order to reduce the pain. It is linked to poor sleep quality and wakefulness.

1.2.2.3 *Emotional: depression and anxiety*

Thirty to fifty per cent of patients with FMS have a history of suffering from depression or anxiety. In some patients, depression or anxiety may develop as a consequence of suffering from chronic widespread pain. However, in others, depression or anxiety pre-dates the onset of chronic widespread pain, suggesting that the latter may result from emotion/mood disturbances. In these patients, the development of chronic widespread pain is often recognized at a time when their mood is low. It is useful to ask the patients directly whether they associate the chronic widespread pain with depression.

In general, it is useful to ask the patient whether they have any feeling of sadness, feelings of worthlessness or emptiness, lack of enjoyment in activities that once were pleasurable, poor

appetite, and suicidal thoughts. Patients with frequent suicidal thoughts need urgent assessment by mental health specialists.

Depression is often accompanied by fatigue, high pain score, and poor coping and disturbed sleep.

Anxiety often coexists with depression in patients with FMS. It can make existing symptoms worse, especially if the diagnosis is delayed, and patients become increasingly concerned and frustrated. In severe cases, patients may complain of panic attacks. Symptoms often associated with anxiety include dizziness, excessive sweating, shortness of breath, dysphagia, palpitation, and tingling sensations.

1.2.2.4 *Stiffness*

Stiffness is a common symptom in patients with FMS. Often this is confused with prolonged early morning stiffness, which is a feature of inflammatory arthritis such as rheumatoid arthritis. In FMS, whilst stiffness starts in the morning, it lasts the whole day and does not improve with activity. The latter is uncommon in inflammatory arthritis, unless the disease is highly active.

1.2.2.5 *Dyscognition*

Patients with FMS often report problems with cognition. Symptoms include problems with memory; inability to concentrate and focus on tasks; trouble in retaining new information; and difficulties with doing mental arithmetic, problem-solving, and learning new tasks. In the United States, the term 'Fibrofog' has been used to describe this problem in cognition, because sufferers often describe a feeling of being in a fog. They are often episodic and typically last for a few days, although, in some cases, it may be more prolonged.

Dyscognition often leads to difficulty at work and problems in carrying out normal household chores. It has a major impact on quality of life and functionality, especially in patients whose work is mentally demanding. It is a major contributor of frustration and psychosocial stress.

1.2.2.6 *Functional disability*

Most patients with FMS have difficulties coping with work and household chores. Both physical and mental difficulties contribute to disability and reduction in quality of life, including work, home, and social relationships, which, in turn, increases psychosocial stress. Assessing these in the medical history is important for formulating a management plan.

1.2.3 **Other symptoms**

In addition to pain and major symptoms, individuals with FMS may suffer from a myriad of other symptoms. Although the physiological basis of these symptoms remains incompletely understood, increasing evidence implicates psychosocial stress and dysfunction of the autonomic nervous system in the pathophysiology.

Many patients complain of tissues feeling swollen, as well as numbness and tingling in upper and lower limbs, although objective evidence is often lacking.

Chronic headaches, chest pain, shortness of breath, and palpitations are common. These are often the result of anxiety, but a careful cardiovascular evaluation should be carried out to exclude serious cardiac illnesses.

Gastrointestinal symptoms, such as nausea, vomiting, bloating, abdominal pain, diarrhoea, and constipation, are common and often related to irritable bowel syndrome.

Uro-gynaecological symptoms, including urgency, frequency, incontinence, pelvic pain, and dysmenorrhoea, are also common.

Unexplained weight loss or gain, and fever are 'red flag' symptoms and strongly suggest alternative diagnoses.

1.3 Clinical features: physical examination

The goal of the physical examination is to confirm diagnosis and rule out other differential diagnoses and systemic diseases. Hence, a full medical examination is important. In patients with FMS, clinical findings are usually unremarkable. Examine the patient's gait, range of joint movement, and deformities. Objective evidence of muscle weakness, synovitis, heart murmur, slow tendon reflexes, or other neurological abnormality would strongly suggest other diseases, such as hypothyroidism and myopathies, which require further detailed investigation. Osteoarthritis and tendonitis are common incidental findings.

1.3.1 Tender points and tenderness: hyperalgesia and allodynia

The presence of multiple hyperalgesic tender points is a typical finding in FMS. When sufficient pressure/stimulus is applied over any part of our body, pain is experienced. This is normal nociception. Patients with FMS have reduced pressure pain threshold, experiencing pain with a normally innocuous pressure—allodynia. When a noxious stimulus or pressure is applied, patients with FMS experience more severe pain than normal individuals—hyperalgesia. A more detailed explanation of the pathophysiology of hyperalgesia and allodynia is given in Chapter 3. Eliciting these tender points helps to establish the diagnosis of FMS.

1.4 American College of Rheumatology classification criteria for fibromyalgia syndrome

1.4.1 American College of Rheumatology 1990 classification criteria

To facilitate research to ensure similar patient cohorts are recruited, the ACR published the 'classification criteria' for the diagnosis of FMS in 1990. It stipulates two basic requirements:

1. First, the presence of chronic widespread pain defined as pain in all four quadrants of the body, as well as in the axial skeleton, for at least 3 months on a more or less continuous basis.
2. Second, the presence of at least 11 of 18 anatomically specific tender points. They include nine sites bilaterally: occiput, low cervical, supraspinatus, trapezius, second rib, lateral epicondyle, gluteal, greater trochanter, and medial knee.

These naturally occurring sites are uncomfortable to firm digital pressure in normal individuals, but, in FMS, similar pressure elicits marked tenderness and often a wince/withdrawal response. The thumb should be used to apply pressure to the site. A tender point hurts only at the area where pressure (enough to cause the examiner's nail bed to blanch, or about 4 kg) is applied. These must be reported as 'painful', not just 'tender' (Figure 1.1, Table 1.1).

1.4.2 American College of Rheumatology 2010 preliminary diagnostic criteria

In 2010, ACR published preliminary diagnostic criteria for FMS. Its aim was to establish simple, practical criteria for clinical diagnosis of FMS that did not require a tender point examination and to provide a severity scale for FMS. The ACR 2010 preliminary criteria require the presence of widespread pain for at least 3 months and the absence of conditions that may explain widespread pain. Physical examination was replaced by Widespread Pain Index (WPI) (see Section 6.1.3) and Symptom Severity Scale (SSS) (see Section 6.1.4).

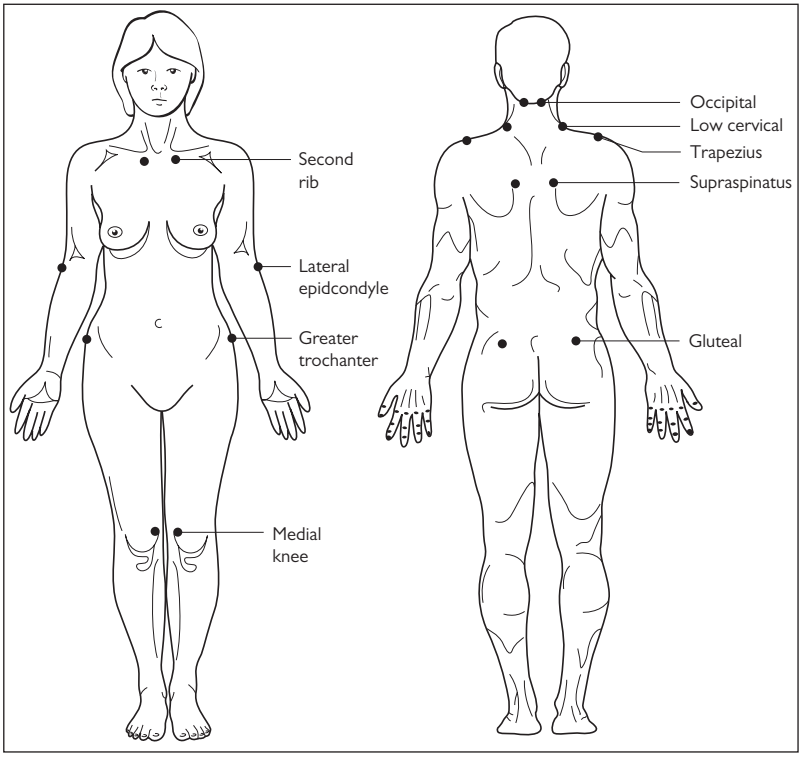

Figure 1.1 American College for Rheumatology (ACR) classification criteria for fibromyalgia (FM): tender point sites. ACR classification criteria for FM: tender point sites are listed in Table 1.1.

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In the WPI, patients indicate the regions of the body (19 regions in total) in which pain has been experienced during the past week. Each positive region is given a score of 1 (WPI ranges from 0 to 19).

The SSS consists of three symptoms: fatigue, waking unrefreshed, and cognitive symptoms, plus the severity of somatic symptoms. These are scored between 0 and 3:

- 0 = no problem/symptom
- 1 = slight or mild problems, generally mild or intermittent, few symptoms
- 2 = moderate, considerable problems, often present and/or at a moderate level, symptoms
- 3 = severe: pervasive, continuous, life-disturbing problems over the last week, a great deal of symptoms.

The maximum total SSS score is 12.

Permissible somatic symptoms include: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper

Table 1.1 American College of Rheumatology classification criteria for fibromyalgia: tender point sites
Anatomical location
At the nuchal ridge, laterally one-thumb width to the insertion of the suboccipital muscle to the occiput
At the fifth through to the seventh intertransverse spaces of the cervical spine
At the craniomedial border of the scapula at the origin of the supraspinatus
At the upper border of the shoulder in the trapezius muscle midway from the neck to the shoulder joint
In the pectoral muscle at the second costochondral junctions
Approximately three-finger breadths (2 cm) below the lateral epicondyle
In the upper outer quadrant of the gluteus medius
Just posterior to the prominence of the greater trochanter at the piriformis insertion
At the medial fat pad proximal to the joint line
Reproduced with permission from Wolfe F, Smythe HA, Yunus MB, *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum*, 1990; **33**: 160–72.

abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

A patient satisfies the criteria for FMS if the following conditions are met:

- WPI >7 and SSS score >5, or
- WPI 3–6 and SSS score >9.

Removing the need for tender point count is an advantage of the ACR 2010 preliminary diagnostic criteria. However, the SSS is scored by a physician and is time-consuming due to the number of somatic symptoms. Later, modified ACR 2010 preliminary criteria were published which replaced the physician-assessed SSS by three self-reported symptoms, and a 0–31 Fibromyalgia Symptom scale (FS) by adding the WPI to the modified SSS. The major advantage of the modified ACR 2010 diagnostic criteria for FMS is a reduction in physician assessment. However, a recent epidemiological study compared these criteria and found that they defined patient populations; in particular, the modified 2010 criteria increased prevalence from 1.7% to 5.4%, and the female/male ratio from 14:1 to 2:1, when compared with the ACR 1990 classification criteria. In this study, the modified criteria were less specific and classified more men as having FMS. Hence these criteria could not replace the ACR 1990 classification criteria but represent an alternative method of identifying patients.

1.5 **Differential diagnoses**

The list of differential diagnoses includes diseases which may cause widespread pain and weakness:

- Primary generalized osteoarthritis
- Polymyalgia rheumatica

- Rheumatoid arthritis
- Autoimmune connective tissue diseases such as systemic lupus erythematosus and inflammatory muscle diseases
- Myopathies
- Hypothyroidism
- Malignancies.

Sometimes FMS may occur concomitantly with osteoarthritis, rheumatoid arthritis, hypothyroidism, and autoimmune connective tissue diseases. In such cases, the diagnosis of FMS should be considered when the severity of pain does not correlate with disease activity.

The following are a list of 'red flag' symptoms and signs suggestive of alternative diagnosis:

- Symptoms:
  1. Significant changes in weight
  2. Fever
  3. Sleep apnoea (loud and excessive snoring).
- Signs:
  1. Joint swelling
  2. Muscle weakness
  3. Abnormal gait
  4. Skin rashes
  5. Delayed tendon reflexes
  6. Lymphadenopathy
  7. Focal neurological signs.

1.6 **Investigations**

Laboratory and radiological investigations in FMS are used to exclude differential diagnoses.

The list of blood tests should include:

1. Full blood count (FBC)
2. Erythrocyte sedimentation rate (ESR)
3. Biochemistries
4. Liver function test
5. Thyroid function test
6. Muscle enzymes (creatine phosphokinases)
7. Rheumatoid factor and auto-antibodies tests should be performed, especially if rheumatoid arthritis or autoimmune connective tissue diseases are suspected. However, a false positive rate is significant.

Radiological examination is generally unnecessary.

Muscle weakness or an abnormal neurological examination may require nerve conduction study and electromyography.

1.7 Associated conditions

In the past, the term 'secondary fibromyalgia' was used when FMS superimposed upon pre-existing painful conditions such as osteoarthritis or rheumatoid arthritis. When it affects individuals without other chronic painful conditions, it is referred to as 'primary fibromyalgia'. However, the ACR classification criteria do not separate primary and secondary FM.

1.8 Overlap with somatization

FMS shares many common features with, and often coexists with, other syndromes, such as irritable bowel syndrome, chronic fatigue syndrome, and dysmenorrhagia, leading to the suggestion that it is part of a spectrum of disorders characterized by somatization. Indeed, patients with FMS often score highly on anxiety and depression questionnaires. However, many patients with FMS are not depressed, and clinical response to antidepressants is often independent of changes in mood.

1.9 Controversy

In the past, the diagnosis of FMS has been disputed by some clinicians. They have argued that FMS is not a distinct disease entity, and labelling patients with FMS would encourage a chronic illness state and increase healthcare utilization. The overlap with somatization was used to support their argument.

However, it is clear the patient problem of FMS has been recognized for many years. Medicine has a bias towards a pathological explanation of 'disease', and these conditions have often been considered expressions of psychological disturbance of little medical interest. Such symptoms and disability, however, are real, not fabricated or imagined, and reflect a 'functional', rather than 'pathological', abnormality. Recently, with advances in neuroimaging, especially with functional magnetic resonance imaging (fMRI) scan, such functional abnormality can be objectively assessed and demonstrated in FMS. The condition may not be homogeneous in expression, but this is no different from many medical conditions such as osteoarthritis and rheumatoid arthritis. Research in the United Kingdom has shown that it is an increasing healthcare burden, but using the diagnosis of FM constructively reduces healthcare utilization. Furthermore, effective treatments are available. More detailed explanation will be given in later chapters of this book. Hence, it is a mistake to ignore FMS as a medical problem.

1.10 Summary

Recent research showed that the diagnosis is often delayed for 5 years, and many unnecessary referral and investigations are performed prior to the diagnosis. Prompt recognition and diagnosis are important to both patients and healthcare state. The ACR has established classification criteria which are simple to apply in the routine clinical setting for the diagnosis of FMS.

Useful practical hints

- Ask about the site, duration, onset, and severity of pain.
- Ask patients whether they feel tired all the time.
- Ask patients whether they sleep well and whether they feel refreshed in the morning.
- Ask patients whether they feel depressed, anxious, or pressurized/stressed at home and at work. In patients with depression, ask whether they have any suicidal thoughts. The presence of the latter will need urgent psychiatric assessment.
- Ask patients whether they have any problem with memory, or difficulties with concentration, problem-solving, and learning new tasks.
- Ask about the impact of illness on daily life, work, and social relationships.
- Remember to ask the 'red flag' symptoms: unexplained weight changes and fever.
- Conduct a general medical examination, and assess the number of FM tender points.
- Remember the red flag signs: joint swelling, muscle weakness, abnormal gait, skin rashes, delayed tendon reflexes, and lymphadenopathies.

Suggested reading

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Chapter 2

Epidemiology and healthcare burden of fibromyalgia syndrome

Key points

- Fibromyalgia syndrome (FMS) is common, affecting 2% of the population.
- It is commoner in women than in men, with a gender ratio of 7:1.
- Physical function and quality of life are often reduced. Most patients have chronic disease. Spontaneous remission is uncommon.
- Medical cost is high, up to 10 years prior to diagnosis. Societal cost of FMS due to reduced productivity is high. Constructive diagnosis can reduce healthcare cost.

2.1 History of fibromyalgia syndrome

The first accurate description of FMS appeared in the mid 1800s. In 1850, Froriep reported that patients with 'rheumatism' had hard places in their muscles, which were painful to pressure. The term 'fibrositis' was introduced by Gowers in 1904. He described regional pain syndromes, including sensitivity to light touch, in association with fatigue and sleep disturbances in the absence of any signs of local or systemic inflammation. In the 1930s, Lewis and Kellgren injected hypertonic saline into deep muscle tissue and induced referred muscle pain. The distribution of pain referral patterns was uniform and differed from dermatomal patterns. During the next half-century, fibrositis, as it was then called, was considered by some to be a common cause of muscular pain, by others to be a manifestation of 'tension' or 'psychogenic rheumatism', and by the rheumatology community in general to be a non-entity.

Smythe and Moldofsky introduced the current concept of FMS in the 1970s through studies in which they described certain anatomic locations being more tender in patients with FMS than in controls. These 'tender points' were often identical to those most tender in regional pain conditions such as 'tennis elbow', 'costochondritis', and cervical strain syndromes. Importantly, they first showed that patients with FMS had stage 4 sleep disturbance and that experimental selective stage 4 disturbance led to myalgia, fatigue, and muscle tenderness, consistent with FMS, in healthy volunteers.

Subsequently, the diagnostic utility of tender points was confirmed by studies in the 1980s from different research groups. Many diagnostic criteria were developed, based on the presence of pain, tender points, and other symptoms, and the exclusion of other rheumatic or systemic diseases. However, many observers have noted the concomitant occurrence of FMS with chronic painful rheumatic disease. This led to the introduction of the concept of primary and secondary FMS. Over the years, authors debated the optimal number of tender points, as well as the relevance of the concept of primary and secondary FM. In 1990, the ACR criteria for the classification of FM were published. This was based on a study of 293 patients with FMS and 265 controls. Participants were interviewed and examined by trained, blinded assessors.

Controls were matched for age and sex, and all had a rheumatic disorder that could be easily confused with FM such as 'possible' rheumatoid arthritis. The combination of widespread pain, defined as bilateral, above and below the waist, and axial, and at least 11 of 18 specified tender points yielded a sensitivity of 88.4% and a specificity of 81.1%. There were no significant differences in patients considered to have primary/concomitant versus secondary FM, and, for classification purposes, such distinctions were to be discarded. No exclusions were made for laboratory or radiographic findings. The ACR classification criteria were developed to facilitate research, so that a homogeneous population of patients can be studied, allowing different studies to be pooled or compared. Although they were not designed primarily as diagnostic criteria, they are now widely used as such in routine clinical practice.

2.2 **Epidemiology**

Using the ACR 1990 classification criteria, the prevalence of FMS in the general population ranges from 0.5% to 4%. The prevalence of FMS in medical outpatient clinics is much higher than in the general population and ranges from 10% to 16% in rheumatology outpatient clinics. It can affect children as well as adults. The prevalence of FMS is 5.4% if the modified ACR 2010 criteria were used.

Gender: FMS is 3–7 times commoner in women than in men. The gender ratio tends to be higher in hospital, compared with general population, studies. The female-to-male ratio is 2:1 if the modified ACR 2010 criteria were applied.

Age: FMS may be diagnosed in individuals of all ages. Symptoms usually arise in those aged 20–55 years, but the condition may occur in childhood. In the ACR 1990 classification criteria study, the mean age was 49 years, with 89% of patients being female. This prevalence increased with age, reaching 7% in women aged 60–80 years.

Ethnicity: no racial predilection exists in FMS. Researchers have reported the condition in all ethnic groups and cultures. In the United States, 93% were Caucasian, 5% Hispanic, and 1% black. Comparison between patients with FMS has been made in Europe and the United States. No significant difference in manifestation was found.

2.2.1 **Global prevalence in the general population**

FMS is prevalent in all countries, unrelated to the level of industrialization and local culture. Prior to the publication of the ACR criteria, estimates of the prevalence of FMS varied from 1% to 2% in population surveys. Since the ACR 1990 criteria were published, a number of studies have assessed the point prevalence of FMS by screening questionnaires followed by detail assessments. In Canada, an epidemiological study found that the point prevalence of ACR-defined FMS in the general population was 3%. A similar population-based epidemiological study in Europe—the FEEL study (Fibromyalgia and Epidemiology: European Large-scale survey)—found that the point prevalence of possible FMS in France and Portugal was 7.4% and 10.45%, respectively.

2.2.2 **Population versus clinical practice**

Whilst the population point prevalence of FMS is approximately 2%, FMS accounts for 2.1% attendance in a family practice clinic, 5.7% in a general medical clinic, 5–8% in a hospital setting, and 14–20% in a rheumatology clinic.

2.2.3 **Risk factors**

Many studies have shown that psychological conditions, such as somatization, having a mental disorder, the presence of psychological distress, major depression, panic disorder, and familial

major mood disorder, are risk factors for developing FMS. Previous trauma and sociocultural factors, such as less education, low level of income, being divorced, being disabled, being an immigrant, smoking, and lower social class, have all been implicated, but definitive evidence of causation is lacking.

A number of studies have suggested that genetic factors play an important role in the development of FMS. Twenty-eight per cent of offspring of mothers with FMS suffer from chronic widespread pain. One case-controlled study also found strongly familial aggregation of FMS. The risk of suffering from FMS in a relative of a proband with FMS was increased eightfold when compared with probands of rheumatoid arthritis. A study comparing the prevalence of chronic widespread pain in monozygotic and dizygotic twins found that genetic factors accounted for 50% of the total variance. This provides persuasive evidence supporting the importance of genetic factors in the pathogenesis of FMS.

A number of candidate genes have been suggested which include polymorphisms of genes in the serotonergic, catecholaminergic, and dopaminergic systems. Overall, it is highly likely that polygenetic factors may act in concert with environmental factors in the development of FMS.

2.2.4 **Drawback of American College of Rheumatology classification criteria**

When the ACR 1990 classification criteria were developed, it was thought that there may be local pathologies at the sites of tender points. However, recent research has shown that tenderness is widespread in FMS and can be elicited in many parts of the body. The pathophysiology of increased tenderness will be explained in Chapter 3.

Furthermore, the number of tender point counts correlates more highly with psychological distress than with the tenderness/pressure pain threshold as measured by dolorimetry. The number of tender points is also influenced by gender. Even in healthy individuals, women are more likely to have a higher number of tender points than men. Research has shown that women are 11 times more likely than men to fulfil the ACR 1990 criteria for having at least 11 tender points. This results in the condition being underdiagnosed, and its prevalence underestimated, in men.

A recent study comparing the diagnosis of FMS based on ACR 1990 criteria with clinical findings or surveys found that the agreement was only moderate. It also showed that the cut-off of 11 tender points was insensitive for the diagnosis of FMS. Using six tender points as a cut-off was more sensitive without losing specificity.

The problem with the ACR 1990 classification criteria led to several epidemiological studies using chronic widespread pain as a definition to study this condition in the community. Chronic widespread pain is common. In developed countries, the prevalence of chronic widespread pain is 7–13%, based on population studies in the United Kingdom, Sweden, and North America. Chronic regional pain, such as low back pain, affects 20–25% of the population. Both conditions are commoner in women, with a female-to-male ratio of 1:5. However, chronic widespread pain is only modestly associated with distress, and distress is only weakly associated with the subsequent development of chronic widespread pain. Many people with chronic widespread pain do not have, or subsequently develop, distress or depression. As discussed in Chapter 1, the ACR 2010 criteria were developed to address the weakness of the 1990 criteria.

2.2.5 **Summary of epidemiology**

Both chronic widespread pain and FMS are very common. The prevalence of chronic widespread pain in the community is higher than FMS. In the community, many patients fulfil the ACR classification criteria without the diagnosis being made. Hence, the diagnosis does not create the syndrome, but patients with FMS are prevalent in the community. FMS may

represent a continuum of chronic widespread pain in the population. The impression of a high female-to-male ratio of FMS may be due to the stipulated tender point count threshold by the ACR 1990 classification criteria, which tends to bias against men. FMS is now the second or third commonest disorder that rheumatologists evaluate and treat. Rheumatologists may find that approximately 10–20% of their patients have FMS.

The perception of many clinicians associating FMS with women who have high levels of psychological stress owes much to the ACR 1990 classification criteria stipulation for at least 11 tender points, and many studies have recruited patients with FMS from hospital-based outpatient clinics where psychological and psychiatric co-morbidities are much higher than in the community.

2.3 **Prognosis**

In general, FMS is neither progressive nor fatal. Most studies show that treatment can significantly improve symptoms, function, and quality of life in the short term. In general, children with FMS tend to have better outlooks than adults. Although these studies provide optimism, prospective long-term cohort studies based in tertiary hospitals in North America and Europe found no significant change in prognosis over a 6- to 8-year period. Severity of pain, fatigue, disability, and quality of life remained unchanged.

Furthermore, they found little improvement in health status, health service utilization, and costs, with approximately 25% of patients with FMS receiving disability or other compensation payments. Health status in patients with FMS is at least as poor as, if not worse than, that in those with other musculoskeletal diseases such as rheumatoid arthritis. Predictors of poor outcome include significant life crisis or severe disability. However, patients with FMS in the community may have a milder condition and a better prognosis than those seen in specialist centres. Granges *et al*. reported a remission rate of 24% after 2 years. Other studies found 25–35% of patients with FMS report an improvement in pain over time, although it is rare for symptoms to subside completely.

It is important for patients to realize that complete remission is rare, and there is no simple cure for FMS. They should be encouraged to have a positive attitude and develop better coping strategies with the help of healthcare professionals. Studies have shown that a good outcome is related to having a positive attitude and an effective coping strategy. Resolution of ongoing stress and promotion of the patient's self-efficacy for control of pain are of pivotal importance in maintaining long-term improvement. A notable example is the benefit of regular exercise. One study suggested that patients with FMS who exercise regularly over a period of 4 years have a better outcome. With the lack of a universal panacea, a multidisciplinary approach will be necessary to manage FMS, especially for patients with more severe, or a wide range of, symptoms.

2.4 **Quality of life**

FMS varies significantly in severity. However, the quality of life is generally reduced. Both impaired physical function and emotional impact adversely affect the quality of life. Approximately 50% of all patients have difficulty with routine daily activities, whilst 30–40% have to stop work or change their employment. The lack of support from family, friends, and the healthcare system may further compound the problem. Some have compared the social, emotional, economic, and functional effect of FMS on an individual's life with the effects of rheumatoid arthritis. On a scale of 1–10 (0 = lowest and 10 = highest), the average

'present quality of life' score for patients with FMS was 4.8, although standard generic human-related quality of life instruments may be insensitive to capture quality of life issues for many people with FMS.

2.4.1 **Physical function**

Patients with FMS often find it difficult to perform daily activities. Almost half the patients reported some disability. Many patients complain of stiffness in the morning and need more time to get started. Often they struggle with tasks, which require sustained or repetitive physical effort. This is often aggravated by cold weather.

Quality of life, measured by Medical Outcomes Study Short Form-36 Health Survey, in patients with FMS has been compared with rheumatoid arthritis and healthy individuals. Physical functioning, physical role, social functioning, bodily pain, general health, vitality, emotional role, and mental health scores were significantly lower in rheumatoid arthritis and FMS patients than in control subjects. Patients with FMS had significantly lower mental health scores than rheumatoid arthritis patients. Indeed, psychological factors/mental health seem to play a pronounced disabling role in FMS.

2.4.2 **Mental health/psychological stress**

One study compared the quality of life and general health status of 98 patients with FMS with 48 healthy volunteers using the Nottingham Health Profile. Patients with FMS have significantly higher Nottingham Health Profile scores, indicating a poorer general health status. Nottingham Health Profile scores correlated with disease activity as measured by tender point count, Fibromyalgia Impact Questionnaire (FIQ), and Health Assessment Questionnaire (HAQ) scores. Patients with depression tend to have higher Nottingham Health Profile scores. This suggests an important relationship between pain, depression, and quality of life in patients with FMS. Moreover, the Nottingham Health Profile score correlated with disease duration, suggesting that chronicity may also adversely impact general health and quality of life.

A telephone survey in Spain, based on patients with FMS attending a university hospital, found them to have an average FIQ score of 63.6. Poor quality of life correlated with having a larger number of children, being tired and being in a depressed mood, reference to repercussion on the family environment, and a lower self-rated health. Importantly, those who consulted more specialists before the diagnosis of FMS were associated with a poor quality of life.

2.4.3 **Sleep disturbance and quality of life**

A study in over 100 patients with FMS found that sleep quality was significantly predictive of pain, fatigue, and social functioning. Therefore, interventions designed to improve sleep quality may help to restore health-related quality of life in FMS.

2.4.4 **Risk of negative behaviours**

Severity of pain, poor emotional health, and sleep disturbances, either alone or in combination, may lead to excessive self-medication and overuse of sleeping pills, alcohol, drugs, or caffeine. A study in 2001 found a higher incidence of violent deaths, including suicide and accidents, among people with chronic widespread pain.

Quality of life is poor in patients with FMS; not surprisingly, patients with significant mood involvement fare worse, given the association between worse outcome and prior consultation before diagnosis and chronicity. Prompt diagnosis and positive management may prevent the development of a vicious cycle leading to the condition spiralling out of control.

2.5 **Healthcare burden**

In the United States, the annual direct healthcare cost of FMS in 1996 was $2274 per patient. Hospitalization and day-care services were the main expenditures. Data from the National Center for Chronic Disease Prevention and Health Promotion showed that, in 1997, 7440 hospitalizations were related to FMS. It accounts for 2.2 million ambulatory care visits, 1.8 million physician office visits, 266 000 emergency department visits, and 187 000 outpatient department visits. The average patient makes ten primary care appointments per year and is hospitalized, on average, once every 3 years. The cost of management of FMS in primary care clinics is high because of the diagnostic tests and treatment. Patients with FMS were more likely to be referred to hospital specialists and have diagnostic procedures. Confronted by such statistics, the Chief Medical Officer in the United Kingdom wrote to all doctors in the United Kingdom, emphasizing the healthcare burden of chronic widespread pain and urging that more research and information are essential to address the problem and improve outcome.

When compared to other chronic diseases, such as diabetes mellitus and hypertension, patients with FMS consume healthcare resources to a similar extent, but the latter receive far less attention from the healthcare system. Greater awareness of this disorder can improve management and facilitate planning of healthcare resources, thus improving quality of care. Indeed, a recent study in the United Kingdom supports such premise. Based on the United Kingdom General Practice Research Database, a large database covering 5 million patients found that healthcare utilization in patients with FMS was already very high, compared with disease controls, matched on the diagnosis date, gender, and age, up to 10 years prior to diagnosis. Increase in cost was due to a higher rate of visits, prescriptions, and diagnostic tests. Patients with FMS averaged 25 visits and 11 prescriptions per year, compared with 12 visits and 4.5 prescriptions per year in controls. Following the diagnosis of FMS, the rate of consultations stabilized and then declined to 13 per 100 patients per year by 4 years post-diagnosis (Figure 2.1a). Overall rates of referrals and tests were significantly higher in FMS cases, compared with controls. Following the FMS diagnosis, referral rates declined considerably, and the incidence of tests appeared to stabilize (Figure 2.1b). Rheumatology referrals dropped to near control levels by 4 years following the diagnosis. This is evidence that the diagnosis of FMS, which is made mainly by rheumatologists in the United Kingdom, may be used constructively in the management of FMS.

2.6 **Social cost**

The cost of FMS to both the individual and to society is huge. Approximately one-third of patients with FMS have to adapt their work, shorten their workdays or workweeks, or do both to keep their jobs. Others have to change jobs that are less demanding physically and mentally. This often leads to decreased income and increased financial burdens. The hidden costs of disability and co-morbidities greatly increase the true burden of FMS. A study in Europe showed that the average annual disease-related total societal cost for FMS was €7813 per patient. In the United States, the indirect medical cost in 1997 amounted to $3671. A survey in the United States found that 42% of patients with FMS were employed and 28% were homemakers. The total annual costs for FMS claimants were more than twice as high as the costs for the typical insurance beneficiary. The prevalence of disability was twice as high among FMS employees as overall employees. For every dollar spent on FMS-specific claims, employers spent about $60–140 on additional direct and indirect costs. Twenty to thirty per cent of patients were receiving disability payment, with 16% receiving social security benefits. The estimated overall

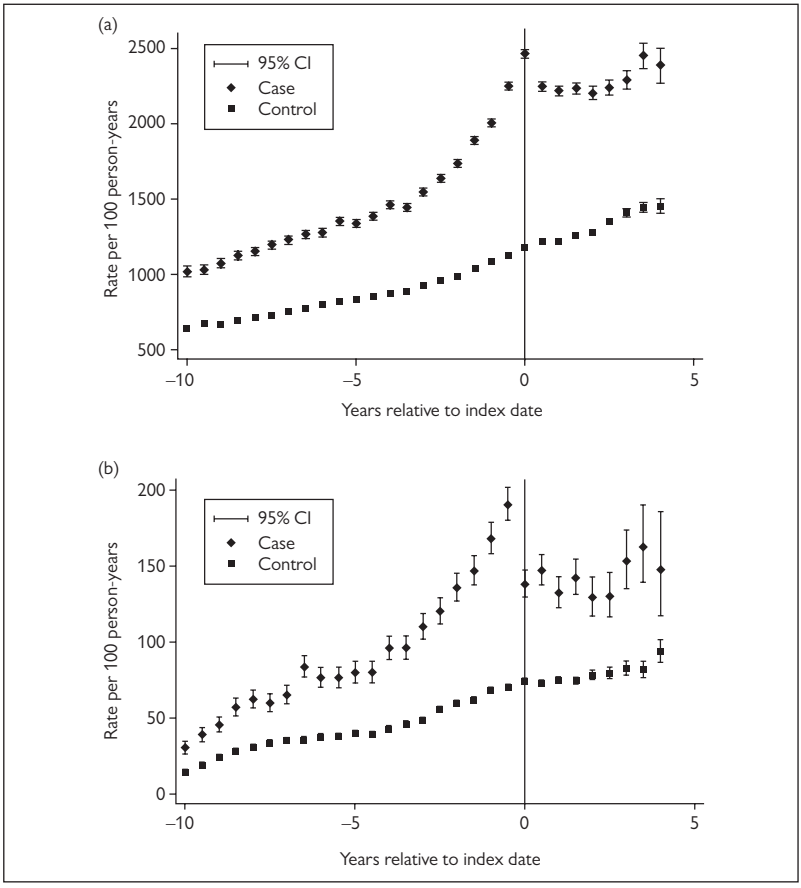

Figure 2.1 The impact of diagnosis of FMS on healthcare cost: (a) total number of clinic visits and (b) number of diagnostic tests.

Reproduced from Hughes G, Martinez C, Myon E, *et al.* (2006). The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. *Arthritis & Rheumatism*, Jan; **54**(1): 177–83.

annual cost of FMS to the economy in the United States is over $9 billion. It accounts for a loss of 1–2% of the nation's overall productivity.

Although the financial cost of FMS is high, the personal/emotional cost to patients, their families, and friends is staggering. Relationships are strained at best and many times are destroyed by this illness.

2.7 **Summary**

FMS is common but under-recognized. Physical disability, and sleep and mood disturbances result in poor quality of life. The direct and indirect medical costs of FMS are high. Whilst the

ACR criteria are not perfect, applying it constructively in routine clinical settings can reduce the healthcare burden of this chronic debilitating condition.

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Chapter 3

Pathophysiology in fibromyalgia syndrome

Key points

- Pain processing is complex and involves nociception, transmission, modulation, and perception.
- Objective examination using function neuroimaging has demonstrated that pain in patients with fibromyalgia syndrome (FMS) is 'real'.
- Physiological pain is important in protection against harm, whilst maladaptive (pathologic) pain is caused by functional abnormalities of the nervous system.
- FMS is characterized by maladaptive pain.
- Sleep study in patients with FMS showed a reduction in slow-wave sleep and increased wakefulness. In healthy volunteers, selective deprivation of sleep can induce myalgia and tender points of FMS.
- Patients with FMS often report experiencing previous stressful or traumatic events. A reduced hypothalamic–pituitary–adrenal axis response to stress can contribute to the development of FMS.

3.1 Introduction

In the past, FMS was often referred to as fibrositis which is a misnomer as -itis implied an inflammatory element. The word 'fibromyalgia' was derived from Latin, meaning a condition of fibro (fibrous tissue), my (muscles), al (pain), and gia (condition of). FM was most commonly known by the misnomer fibrositis where Chaitrow asserts that no inflammatory process has ever been found to be part of this disease. Current research suggests the central pathophysiology of FMS is abnormal central pain processing resulting in central sensitivity.

3.2 Understanding pain

Pain is an important physiological mechanism designed to protect us from harm. It warns us of actual or impending danger or damage. Not surprisingly, it is linked to the stress response and reflex withdrawal to protect from further damage or harm. Absence of pain perception, as occurs in the Charcot joint, results in excessive tissue damage and destruction. In the extreme case, such as what occurs in the rare condition hereditary pain indifferent syndrome, the absence of high-affinity receptors for nerve growth factor (NGF) results in the absence of pain sensation. The condition was characterized by multiple Charcot joints, fracture, and deformities. Undoubtedly, pain has an important physiological role, both for protection against damage and for encouraging rest to allow repair processes to occur.

Pain can be defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage'. Although it is essentially a sensation, pain has strong cognitive and emotional components. It is interpreted as a suffering resulting in psychological and physiological stress. The latter includes avoidance of motor reflexes, alterations in autonomic output, and increased neuroendocrine response. All of these are intrinsic to the pain experience.

3.2.1 **Early theories of pain**

The description of pain has a long history dating back to as far as Babylonian times. Early concepts of pain involved the perception that pain was dangerous. Descartes (1664) was the first person to recognize that there was a signalling system involved in the detection of noxious stimuli (Figure 3.1).

He described how, if a subject puts his/her foot in a flame, pain is detected, and this information is carried to the organ of perception. The sensory experience of acute pain caused by a stimulus is mediated by the nociceptive system. This system extends from the periphery through the spinal cord, brainstem, and thalamus to the cerebral cortex where the sensation is perceived. To prevent damage, we have learned to associate certain categories of stimuli with danger that must be avoided. This is achieved by linking noxious stimuli with a sensation that is intense and unpleasant. The sensation of pain therefore must be sufficiently strong, so that it demands immediate action. This model of pain was developed further by describing how pain is detected by specific nociceptors which detect tissue-damaging stimuli. These stimuli create action potentials which are transmitted via the peripheral nerves to the spinal cord and then to the brain.

The next major breakthrough in the concept of pain was the development of the gate control theory by Melzack and Wall in 1965.

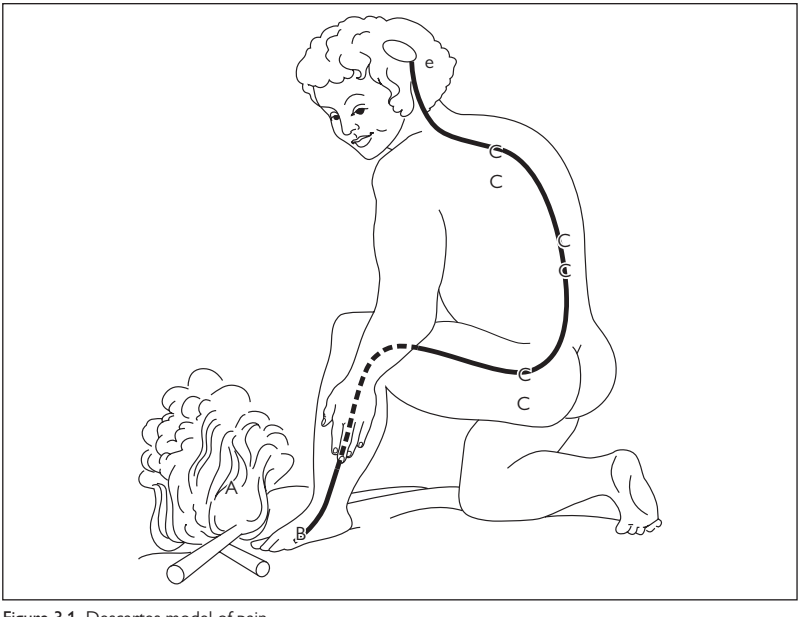

Figure 3.1 Descartes model of pain.
René Descartes (1664). L'homme de René Descartes. Paris: Charles Angot.

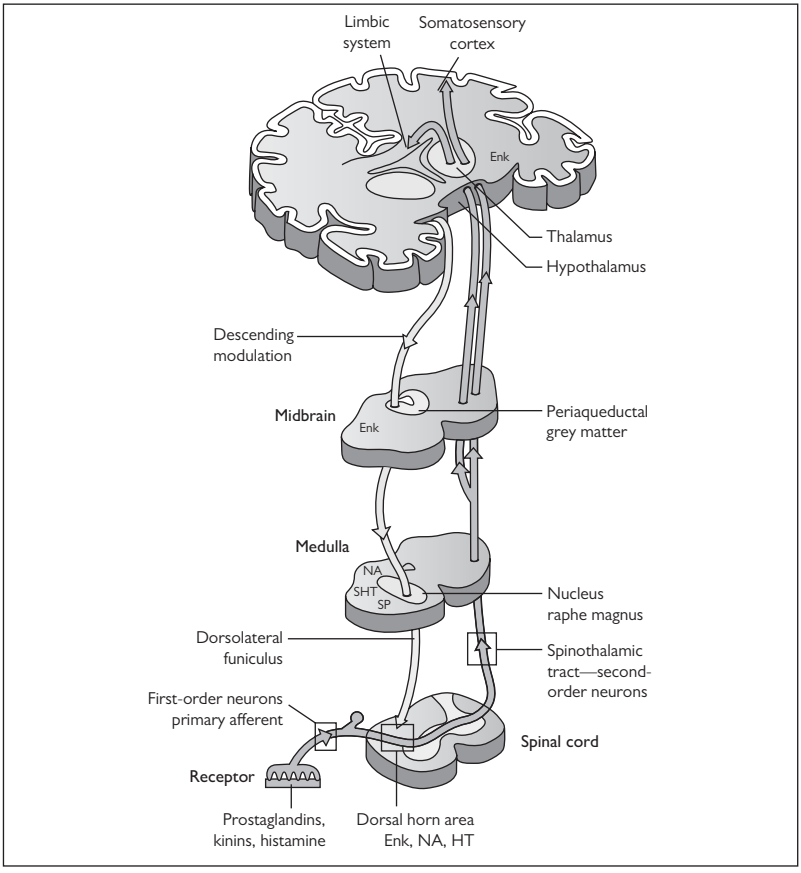

Figure 3.2 The pain pathway.

Reprinted from *Rheumatology*, Third edition, Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, ISBN 0323024041, published by Mosby (2003), with permission of Elsevier.

It introduced the idea that the individual had biomedical mechanisms, which could control how pain was understood and appreciated. Much of this is derived from an understanding of the neurological pain pathway where a stimulus from the periphery travels to the brain (Figure 3.2). In addition, there are inhibitory pathways, which can control pain. The gate control theory describes how pain can be overridden, 'closing the gate' under certain circumstances. The classic case is that of pain resulting from battleground injuries not being registered until the soldier had been carried from the battleground.

Woolf used the terms adaptive and maladaptive to differentiate physiological pain that protects the organism from injury or promotes healing (adaptive) from pathologic pain due to a functional abnormality of the nervous system (maladaptive).

3.2.2 **Current theory of normal pain processing**

Pain processing can be divided into four main parts: nociception, transmission, modulation, and perception.

1. **Nociception**—is the detection of tissue damage or that something is wrong, in which a noxious stimulus is detected by a peripheral nociceptor and converted into an electric impulse in the free afferent nerve ending. This is a strongly physical and physiological process and can be inhibited by NSAIDs, opioids, and local anaesthetics.
2. **Transmission**—is the process whereby nerve impulses are propagated through the peripheral and central nervous systems. Sharp pain is conveyed by A-delta (fast) fibres; dull pain is conducted by C (slow) fibres, and tactile sensation is conveyed by A-beta fibres. All these have a lower threshold of stimulation. Transmission can be inhibited by local anaesthetics and alpha-2 agonists.
3. **Modulation**—occurs mainly in the central nervous system (CNS), first in the dorsal horn cells of the spinal cord. Excitatory neuropeptides, such as substance P, glutamate, and aspartate, amplify the pain signals in ascending projection neurons, whilst endogenous inhibitory descending neurons releasing opioid, serotonin, and noradrenaline dampen the nociceptive response. Local anaesthetics, alpha-2 agonists, opioids, NSAIDs, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and N-methyl-d-aspartate (NMDA) receptor antagonists can affect the balance between pain amplification and inhibition.
4. **Perception**—is the cerebral cortical response to nociceptive signals. It relies heavily on the interpretation of the initial stimulus. This process has huge inter-individual variability—a minimal stimulus in some subjects can result in registering a large amount of pain; conversely, a large stimulus in others can result in no pain being registered. Perception can be inhibited by general anaesthetics, opioids, and alpha-2 agonists.

3.2.2.1 *Nociceptors*

Nociceptors are mostly bare nerve endings, which penetrate past the epidermal/dermal junction and are attached to fine fibres. There are two types of nociceptors: polymodal and high-threshold mechano–heat receptors.

Alternatively, the nociceptors can be classified biochemically into two main categories:

- NGF-dependent nociceptors which account for 70% of receptors. They require NGF for their development and synapse in laminae I and II outer of the spinal cord
- Glial-derived nerve factor-dependent nociceptors which constitute the remaining 30% of receptors. They require glial-derived nerve factor for their development and synapse in lamina III inner. It transduces the effect of a physical stimulus such as noxious heat.

Until recently, it was thought that nociceptors were only found in the somatic region but not the viscera. However, a recent study showed that a distended bladder becomes painful, suggesting that there is a small population of nociceptors in the viscera. In general, visceral pain is less well localized than somatic pain, which may reflect the density of the nociceptors.

3.2.2.2 *Nerve fibres*

Sensory nerve fibres conduct signals from the nociceptors to the spinal cord from various parts of the body. There are at least two major types of nerve fibres thought to be responsible for this process:

- **A-delta nerve fibres**: thought to be responsible for ‘acute’ or ‘fast’ pain, as they carry electrical messages to the spinal cord at approximately 40 miles per hour
- **C fibres**: thought to be responsible for ‘chronic’, ‘slow’, or ‘dull’ pain and which carry electrical impulses at approximately 3 miles per hour.

Some acute injury activates other sensory nerve fibres that conduct even 'faster' than A-delta fibres, which may activate inhibitory pathways in the spinal cord and brain to override some of the pain messages carried by the A-delta and C fibres.

These physiological pain processes apply in many musculoskeletal diseases where nociceptors detecting pain are present in structures such as the synovium, joint capsule, bone, muscles, and ligaments. When nociceptors are activated, pain signals are transmitted by special peripheral nerves to the spinal cord and up to the brain. These messages can be overridden by other signals produced by interventions such as massage, heat or cold packs, transcutaneous nerve stimulation, medications, or even acupuncture.

3.2.2.3 *Spinal cord*

All sensory information enters the spinal cord via the dorsal root. The dorsal horn of the spinal cord is a vital area for sensory processing. It is divided into laminae I–VI. Nociceptors synapse via the superficial laminae.

Numerous pain neurotransmitters are present in the spinal cord. Aspartate and glutamate are the main excitatory amino acids produced by the afferent neurons and are probably the most significant molecules in terms of pain transmission. Their activity is modulated by inhibitory neurotransmitters released by a descending control process. The overall result depends on the balance between excitatory and inhibitory neurotransmitters.

There are four main inhibitory processes in the spinal cord:

- **Endogenous opioids**: act pre-synaptically to prevent the information from reaching the spinal cord
- **Afferent inhibition**: non-noxious stimuli reach the brain much faster than noxious stimuli; therefore, 'the gate' can be closed before the pain message reaches the brain
- **Segmental inhibition**: consists of activation of large afferent fibres subserving epicritic sensation inhibitory neurons and spinothalamic activity. Glycine and gamma-aminobutyric acid (GABA) are the main inhibitory neurotransmitters
- **Descending inhibition**: several supraspinal structures, including the periaqueductal grey, reticular formation, and nucleus raphe magnus, send fibres down the spinal cord to inhibit pain at the level of the dorsal horn. Axons from these structures act pre-synaptically on the primary afferent neurons and post-synaptically on second-order neurons. These inhibitory pathways utilize neurotransmitters, such as noradrenaline and serotonin, on nociceptive neurons in the spinal cord, as well as on spinal inhibitory interneurons which store and release opioids. Noradrenaline mediates this action through alpha-2 receptors. The endogenous opiate system acts via enkephalins and beta-endorphins. These mainly act pre-synaptically, whereas the exogenous opiates act post-synaptically.

3.2.2.4 *Brain*

Until recently, how the brain perceives pain is poorly understood. In the past, pain was thought of as an extension of the sense of touch. Neuronal signals from the dorsal horn of the spinal cord transmit to the specialized areas of the somatosensory cortex via the thalamus. With the advent of functional neuroimaging using the latest technology, such as fMRI, it has become clear that, aside from the somatosensory cortex, many areas of the brain are involved in pain perception. A detailed explanation is beyond the scope of this book. Briefly, there is growing evidence that the parieto-insular cortex is crucial for pain processing in the brain. The area is strongly activated during pain. Lesions in this region can strongly reduce pain perception. Another important area is the caudal part of the anterior cingulate cortex, which has been implicated in the control of motivational behaviours. Activation of this area is linked to perception of the unpleasantness of pain and is accompanied by activation in

several subcortical sites, such as the amygdala, cerebellum, and striatum, whilst other areas of the brain, such as the rostral anterior cingulate cortex (rACC), have been implicated in pain modulation/inhibition.

3.2.3 **Maladaptive pain**

Maladaptive pain may be acute or chronic. One of the key features of maladaptive pain is increased sensitivity or hyper-responsiveness. This indicates that pain perception is not 'hard-wired' but 'plastic' and dynamic. This is mediated by changes in the nervous system response (neuroplasticity) at peripheral and central locations.

Hyperalgesia is defined as an increased response to a normally painful stimulus. When a noxious stimulus is applied to an area on the arm, there will be a small area of active tissue hyperalgesia due to the sensitivity of local nociceptors in the skin. Over a period of a few hours, a larger area of secondary hyperalgesia develops. In the case of inflammation, this results from the release of some inflammatory mediators, which can reduce nociceptor thresholds. This leads to an increased response to painful stimuli—primary hyperalgesia or peripheral sensitization.

Central sensitization refers to an increase in the excitability of spinal neurons.

Central sensitization may result from several mechanisms:

- **Action potential wind-up**: repeated stimulation of dorsal root afferents, including nociceptive C fibres, can elicit a progressive increase in the number of action potentials generated and prolong the duration of the discharge by neurons and interneurons, even after the afferent C fibres input has stopped
- **Receptive field expansion**: dorsal horn neurons increase their receptor field, such that adjacent neurons in neighbouring areas become responsive to stimuli, whether it is painful or not. This is mediated, in part, by the activation of NMDA receptors in dorsal horn neurons
- **Hyperexcitability of flexion responses**: increase the flexion reflex ipsilaterally and contralaterally.

Molecules that have been implicated in central sensitization include substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), cholecystokinin, angiotensin, galanin, glutamate, and aspartate. These substances trigger changes in membrane excitability, leading to increased intracellular calcium concentration. For example, glutamate and aspartate activate the NMDA receptor and resultant intraneuronal elevation of calcium, which stimulates nitric oxide synthase to produce nitric oxide. The latter is a gaseous molecule that diffuses out from the neuron and stimulates the formation of cyclic guanosine monophosphate (cGMP) in neighbouring neurons. Nitric oxide has been implicated in the development of hyperexcitability, resulting in hyperalgesia or allodynia.

3.2.4 **Maladaptive pain in fibromyalgia syndrome**

A characteristic feature of FMS is hyperalgesia (increasing the response to low-level noxious stimuli) and allodynia (painful response to normally non-noxious stimuli). These are likely to be the result of central sensitization. There are several lines of evidence to suggest that the pain experience of patients with FMS is, in part, the result of disordered pain processing at a central level.

3.2.4.1 *Evidence from somatosensory stimulation*

Secondary hyperalgesia, pain elicited from uninjured tissues around the site of pain, was found to be increased in patients with FMS, compared to controls. When an electric stimulus was applied to the skin, patients with FMS had reduced pain threshold, and pain was noted both distally and proximally to the stimulator, lasting up to 20 minutes after the stimulation was terminated.

Patients with FMS have reduced central inhibitory response. Downregulation of pain threshold can be demonstrated in normal individuals by subjecting them to repeated skin stimulation. When this was compared in female patients with FMS and age-matched healthy women, concurrent tonic thermal stimuli, at both painful and non-painful levels, significantly increased the pain threshold in the healthy subjects, but not in the patients with FMS.

When hypertonic saline was injected into the anterior tibial muscle, patients with FMS experienced a longer duration and a larger area of pain than healthy age-matched controls. Pressure pain and the intramuscular summation pain threshold were significantly lower in patients with FMS.

3.2.4.2 *Evidence from cerebrospinal fluid*

Substance P

Substance P lowers the threshold of synaptic excitability and sensitizes second-order spinal neurons. Two studies have shown a threefold increase of substance P in the CSF of patients with FMS, compared with controls.

Serotonin

Serotonin is a neurotransmitter implicated in sleep, pain perception, headaches, and mood disorders. It is released by some inhibitory neurons. Lower-than-normal levels of serotonin have been observed in patients with FMS.

Nerve growth factor

NGF is critical for the differentiation, maintenance, and survival of sensory neurons. It enhances the production of substance P in afferent neurons, increasing the person's sensitivity or awareness to pain. In some studies, NGF was four times higher in the CSF of patients with FMS than in controls.

3.2.4.3 *Evidence from function neuroimaging*

Functional CNS changes can be demonstrated by several different imaging techniques. It is interesting that chronic pain states have been associated with reduced thalamic blood flow, whereas acute pain increases thalamic blood flow. The reason for this difference is postulated to be a disinhibition of the medial thalamus, which results in activation of a limbic network. Mountz *et al*. reported that patients with FMS had a decreased thalamic and caudate blood flow, compared with healthy controls, on single-photon emission computed tomography imaging.

Altered pain processing has also been demonstrated by studies using fMRI where painful pressure stimuli result in increased cerebral blood flow in areas associated with activation by noxious stimuli; and this is exaggerated in patients with FMS at stimulus intensities that are non-noxious in normal individuals, implying that they have reduced pressure pain threshold.

Neuroimaging using fMRI and positron emission tomography (PET) in two independent studies has implicated abnormalities in the rACC, a region of the brain linked to the descending pain inhibitory pathways, in patients with FMS, compared with age-matched controls. Patients with FMS have reduced activity in the rACC in response to pain. PET imaging found reduced μ-opioid receptor binding potentials in the rACC and other areas of the brain in patients with FMS, compared with controls.

Taken together, there are substantial amount of evidence to suggest that abnormal pain processing is important in the pathophysiology of FMS.

3.3 **Sleep**

One of the most important advances in the understanding of FMS is the association with sleep disturbance. Most patients with FMS complain of non-restorative sleep. Sleep study in patients with FMS has confirmed that reduced sleep quality is associated with non-dreaming,

non-rapid eye movement (non-REM) sleep with interruption by alpha waves and reduction in short-wave sleep, which is important to restoration. In healthy volunteers, selective deprivation of non-REM sleep can induce symptoms and hyperalgesic tender sites of FMS. Recently, it has been shown that sleep deprivation can lead to impaired descending inhibitory pain pathways, which may lead to central sensitization and myalgia. An epidemiological study has also shown that normal individuals who suffer from non-restorative sleep are more likely to develop FMS. Improving sleep quality has been shown to reduce pain and improve fatigue in clinical trials.

3.4 Hypothalamic–pituitary–adrenal axis

Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis has been implicated in the pathophysiology of FMS. The HPA axis is a critical component of the stress adaptation response, which includes various body processes such as digestion, the immune system, mood, and energy. In a normally functioning system, corticotropin-releasing hormone (CRH) stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH then stimulates the adrenal cortex to produce glucocorticoids, which are powerful mediators of the stress adaptation response. The normal circadian rhythm for the release of these hormones leads to a rapid increase in the cortisol level after wakening, reaching a peak within 30–45 minutes. It then gradually falls over the day, rising again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night. Stress induces the release of CRH from the hypothalamus, which is influenced by blood levels of cortisol and by the sleep/wake cycle. Increased production of cortisol mediates responses to stress, allowing the body to attempt countermeasures. However, excess cortisol can be damaging. Atrophy of the hippocampus in humans and animals exposed to severe stress is believed to be mediated by prolonged exposure to high concentrations of cortisol.

Anatomical connections between brain areas, such as the amygdala, hippocampus, and hypothalamus, facilitate the activation of the HPA axis. Sensory information arriving at the lateral aspect of the amygdala is processed and conveyed to the central nucleus, which projects to several parts of the brain involved in responses to fear. At the hypothalamus, fear signalling impulses activate both the sympathetic nervous system and the modulating system of the HPA axis. Deficiencies of the hippocampus may reduce the memory resources available to formulate appropriate reactions to stress.

In patients with FMS, a reduced HPA axis response to stress has been demonstrated. The main HPA abnormalities in FMS are as follows:

- Low free cortisol levels in 24-hour urine samples
- Loss of the normal circadian rhythm with elevated evening cortisol level
- Insulin-induced hypoglycaemia associated with an overproduction of pituitary ACTH
- Low levels of growth hormone
- Insufficient adrenal release of glucocorticoids to stimulation by ACTH.

Patients with FMS often report experiencing a previous stressful or traumatic event. A reduced HPA axis response to stress can contribute to FMS development or worsening of FMS. The HPA axis is also linked to the autonomic nervous system, which is involved in modulating sleep, mood, pain, and cardiovascular activities (including microcirculation of muscles). This could explain many clinical features and the association of FMS with the sympathetic nerve system over activity, although more detailed mechanistic studies will be needed to confirm a causative relationship.

Furthermore, patients with FMS frequently complain that pain and tenderness are worse in the morning and experience significant morning stiffness; this is lessened after nights when

they have had more restful sleep. Although a cause and effect relationship has not been established, a dysfunctioning HPA axis may be an important factor in the pathophysiology of these symptoms in FMS.

The neurotransmitter serotonin has a role in regulating the circadian rhythm and the stress-induced stimulation of the HPA axis. This may partly explain the abnormalities of the HPA axis in FMS. Alternatively, dysfunction of the HPA axis may exaggerate the effects of abnormal serotonin metabolism, resulting in low serotonin levels associated with FMS.

Dysfunctional HPA axis has been implicated in the pathophysiology of many disorders, including anxiety, depression, post-traumatic stress disorder, chronic fatigue syndrome, sleep disturbances, and irritable bowel syndrome. HPA abnormalities may reflect merely other co-morbidities.

3.5 **Summary**

Although the pathogenesis of FMS is not completely understood, the currently known abnormalities substantiate the proposal that FMS can no longer be considered a subjective pain condition. Somatosensory abnormalities, CSF studies, and functional neuroimaging all lead to a whole body of evidence suggesting that maladaptive pain response is at the core of FMS. Ongoing research will continue to provide a clearer picture of the pathophysiology of this complex syndrome.

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Chapter 4

Assessing fibromyalgia syndrome

Key points

- A large number of instruments have been used in the assessment of fibromyalgia syndrome (FMS).
- Visual analogue scale (VAS) of pain can be used to assess pain intensity in the clinical setting, although there are more sophisticated tools.
- Tenderness/pressure pain threshold can be measured by a simple tool such as a dolorimeter.
- Fibromyalgia Impact Questionnaire (FIQ) is a validated multidimensional tool that assesses many major features of the condition.
- Hospital Anxiety and Depression Scale (HADS) is a simple and useful self-completed screening questionnaire for mood disturbances in patients attending routine outpatient clinics. It can be useful in identifying patients with severe depression, which needs referral to a mental health specialist.
- Using a combination of these assessment methods, subgroups of patients with FMS could be identified. These could be used to guide treatment.

4.1 Introduction

In musculoskeletal diseases, many assessment tools/instruments currently used in routine practice were developed initially for research. As such, they were designed to have the properties to aid understanding of the disease pathophysiology or to determine whether interventions are effective. For routine clinical practice, assessments are often performed to determine disease severity, especially if there are predictors of important outcomes and co-morbidities, as well as to identify subsets of patients in whom the result of the assessment helps to inform the choice of treatment and subsequent response to therapy. Given these different objectives, not all instruments used in research are suitable for clinical practice. A good assessment tool needs to have certain characteristics. First, it needs to truly measure what it intends to measure. Second, it must be sufficiently specific and also sensitive to change. Third, it should be feasible to carry out the assessment. Hence, a valid, sensitive, and specific assessment tool, which requires 60 minutes to complete, will be feasible in the setting of research, but impractical for routine outpatient clinics.

4.2 Assessment tools in fibromyalgia syndrome

Numerous instruments have been used in clinical trials of FMS. In part, this is due to a lack of consensus on what should be measured. Most of these instruments have been developed and validated for use in other conditions such as other chronic painful diseases, sleep disorders,

depression, and anxiety. The only exception is the FIQ, which was developed specifically for FMS as a tool to assess symptoms of disease, function, and quality of life.

Since FMS is a complex condition with multiple symptoms, determining which components should be assessed is not straightforward. Consequently, a working group on FMS was convened under the auspices of the Outcome Measures in Rheumatology Arthritis Clinical Trials, an organization whose mission is to foster a global consensus and develop outcome measurements for clinical trials. In 2009, the core data set for FMS was published; these include pain, patient global assessment of disease, fatigue, tenderness, multidimensional function, and sleep. Depression and cognition were recommended but not mandatory.

4.2.1 **Pain**

Obviously, pain is the dominant symptom in FMS. Pain has been measured by many instruments. All of them are based on patient-reported severity. The commonest and simplest methods are the paper-based visual analogue scale (VAS) and numeric rating scale. In clinical trials, there is a need to assess accurately changes in pain intensity over time. The McGill Pain Questionnaire and Brief Pain Inventory are validated questionnaires, which have been used extensively in chronic painful conditions. Both have been used in clinical trials of FMS.

4.2.1.1 *Visual analogue scale and numeric rating scale*

VAS and numeric rating scale often ask patients to rate the average, minimal, and maximal pain intensity during a defined period: 24 hours, last week, or last month. However, the memory of pain intensity is not accurate enough, resulting in significant measurement errors. Such recall bias or error could be reduced by using questions that relate to specific activities collected in a diary. Better still, a real-time electronic diary, using alarms to remind patients to score pain severity at fixed times, was found to be superior to the paper-based method. However, such method may not be feasible in routine clinical practice.

4.2.1.2 *McGill Pain Questionnaire*

The McGill Pain Questionnaire assesses the detailed character of the pain experience by letting patients choose appropriate words describing the distinctive aspects of pain and categorize pain into sensory, affective, evaluative, and miscellaneous sensory components. These are then used to calculate a pain rating index. However, it is fairly lengthy with 76 questions in total. A shortened version Short Form-McGill Pain Questionnaire has only 15 items in the sensory and affective categories that have been validated in FMS and shown to distinguish FM pain from other rheumatic conditions.

4.2.1.3 *Brief Pain Inventory*

The Brief Pain Inventory assesses not only the intensity and quality of pain, but also how the impact interferes with activity, and therefore elements of quality of life. It is a 15-item questionnaire which was developed originally for assessing pain intensity in patients with cancer and how it interferes with the patient's life. Patients are asked to rate the extent that pain interferes with their life on a 0–10 scale across seven domains: general activity, walking, mood, sleep, work, relations with other persons, and enjoyment of life. More recently, it has been used in clinical trials of non-malignant chronic painful conditions, including FMS, in which it has been shown to be feasible and sensitive to change.

4.2.1.4 *Pain drawing*

Although patients with FMS complain of widespread pain, the extent of pain over the body is not constant, hence the interest in assessing the location of pain over time. One common method to evaluate this is by pain drawings. Patients are asked to shade the painful areas of

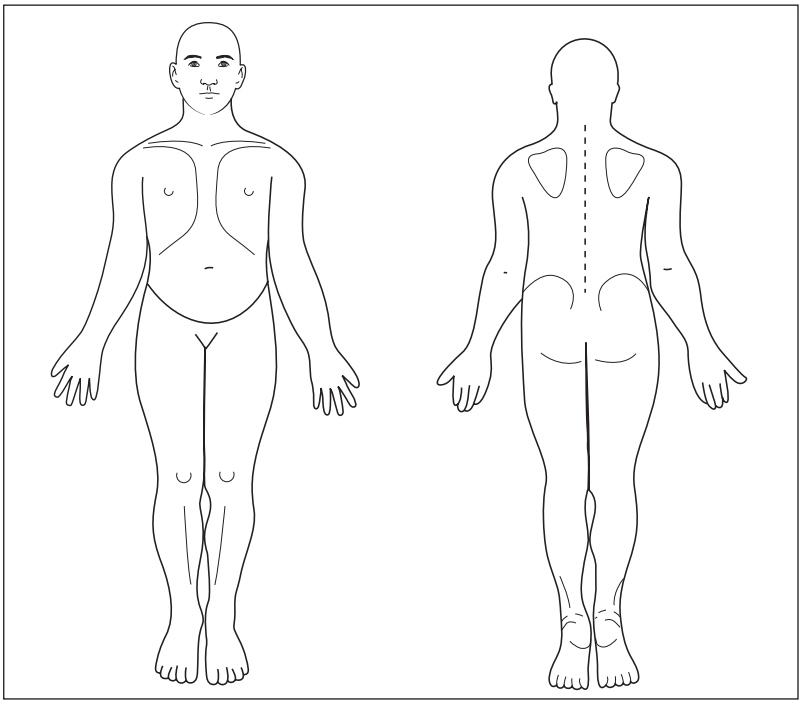

Figure 4.1 Mannequin for pain drawing.

their body on mannequins (Figure 4.1). This method has been used not only in assessing efficacy in clinical trials, but also in population surveys as a screening tool for patients with FMS. Individuals who shade all four quadrants on the mannequins are deemed to have widespread pain. Interestingly, patients with FMS tend to highlight non-articular areas, whilst patients with rheumatoid arthritis tend to restrict their score to joint areas.

4.2.2 **Tenderness**

Intuitively, tenderness may seem to relate to pain. However, spontaneous self-reported pain and stimulus-evoked pain are mechanistically different. The latter is an indication of hyperalgesia and allodynia. Two commonly used methods to assess tenderness in FMS are tender point count and dolorimetry.

4.2.2.1 *Tender point count*

Although the number of tender points is part of the ACR 1990 classification criteria, its role in the assessment of FMS remains unclear. Some researchers have found that tender point count is a crude measure of allodynia to pressure, since it is affected by psychological distress and produces higher score in females.

Others have found that tender point count correlates with pain intensity measured by VAS and neuropathic pain score, but not with anxiety, depression, or somatization; therefore, it was argued that it is included as a marker for the severity of neuropathic pain. In many studies, the number of positive FM tender points is included as part of disease activity assessment; a more

detailed evaluation, which includes the severity of the tenderness at each site, is included in the *Manual tender point survey*. As an outcome measure in clinical trials, tender point count is feasible and sensitive to change.

4.2.2.2 *Pressure pain threshold measurement*

Pressure algometry measured by a dolorimeter (Figure 4.2) is a semi-objective quantitative method to assess pressure pain threshold. It has been used in clinical trials, as well as in routine practice. Compared to healthy controls, patients with FMS exhibit lower pressure pain thresholds which are not restricted to the tender points, suggesting generalized allodynia to pressure. However, the exact methodology is not standardized, but some researchers have found that assessments of three-paired tender point sites provide a representative value for the average pressure pain thresholds.

There are numerous methods that have been developed to understand the pathophysiology of pain in FM. Most of these are beyond the scope of this book, because they are currently not applicable either to clinical trials or to routine practice.

4.2.3 **Fatigue**

Fatigue is a common feature of FMS. Since fatigue is common in many medical illnesses and musculoskeletal conditions, a number of instruments validated in other diseases have been used in clinical trials of FMS. These can be divided into two broad categories: unidimensional and multidimensional. Unidimensional instruments measure intensity without exploring the underlying cause or impact of fatigue.

The commonest unidimensional instruments used are VAS, Functional Assessment of Chronic Illness Therapy Fatigue Scale, and Fatigue Severity Scale. The Functional Assessment of Chronic Illness Therapy Questionnaire is a generic health instrument, which has a fatigue domain. The 13-item questionnaire for the fatigue domain has been used extensively in the clinical trial of inflammatory arthritis. The Fatigue Severity Scale was originally developed for multiple sclerosis and systemic lupus erythematosus; in clinical trials of FM, it was sensitive to change.

Multidimensional instruments for measuring fatigue that have been used in clinical trials in FMS include Multidimensional Assessment of Fatigue and Multidimensional Fatigue Inventory.

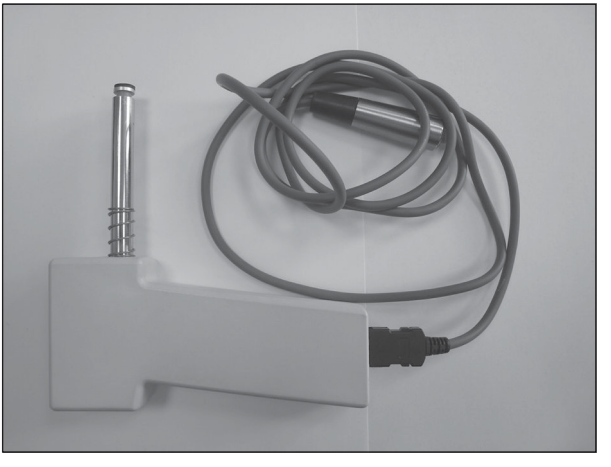

Figure 4.2 A dolorimeter.

The former is a 16-item instrument measuring four dimensions of fatigue: severity, distress, degree of interference in activities of daily living, and timing. The Multidimensional Fatigue Inventory is a 20-item self-report instrument and contains five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. It was developed initially for assessing fatigue in patients with cancer but has been used in musculoskeletal diseases.

4.2.4 **Sleep**

Non-refreshed sleep is common and thought to be an important pathological feature in FMS. Objective and detailed evaluation to assess sleep quantity by polysomnography is not feasible for multicentre clinical trial or routine practice. However, it can be used in mechanistic studies.

Commonly, VAS has been used to assess sleep quality, anchored by 'sleep is no problem' at one end and 'sleep is a major problem' at the other. A similar scale is used on the 'restedness' domain in the FIQ.

The Medical Outcome Sleep Scale, Pittsburgh Sleep Quality Index, and Jenkins Sleep Questionnaire provide more detailed assessment of both sleep quality and quantity. All have been used in clinical trials in FMS, although they have not been validated against findings from polysomnography studies. A 17-item Sleep Assessment Questionnaire has recently been shown to be an excellent screening questionnaire for identifying people with FMS.

Actigraphs are small devices worn on the wrist or ankle that monitor and record movement. They have been used to assess sleep–wake cycles. Since actigraphs can be worn for weeks, or even months, they have been used to assess sleep in many different sleep disorders. In FMS, actigraphy has been shown to correlate with self-reported sleep quality and fatigue.

4.2.5 **Multidimensional function and health-related quality of life**

In chronic diseases, curative treatments are unavailable, but many therapies reduce disease severity, improve symptoms and signs, and make patients 'feel better'. Such improvement is usually reflected in physical function, emotional well-being, and participation in family, work, and social life. This is the rationale for measuring generic health status and health-related quality of life. The latter has been defined as those attributes valued by patients and include their resultant comfort or sense of well-being; the extent to which they were able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities within the family, in the workplace, and in the community. By definition, health-related quality of life instruments are multidimensional and hierarchical with measurement of symptoms, function, physical and mental health, as well as social, vocational, and social participation. Such instruments can be disease-specific or generic. The latter is often used in health economic evaluation, as the benefit of different interventions in a wide range of medical conditions can be compared.

4.2.5.1 *Fibromyalgia Impact Questionnaire*

FIQ is a disease-specific 20-item self-report instrument. It is the most commonly used multidimensional disease-specific instrument in FMS. It has eight domains: physical functioning, days well, work, pain, fatigue, morning stiffness, anxiety, and depression. Although the FIQ is a validated instrument and is extensively used in clinical trials, its sensitivity to changing and scaling properties, especially its ability to assess physical function, has been questioned.

4.2.5.2 *American College of Rheumatology 2010 preliminary criteria Symptom Severity Scale*

As discussed in Chapter 2, the SSS of the ACR 2010 criteria was developed to allow monitoring of symptoms of FMS. It has been used in epidemiological studies, but its use in clinical trials has been limited.

4.2.5.3 *Medical Outcomes Short Form-36 Health Survey*

The Short Form-36 (SF-36) is one of the commonest generic health status instrument used in clinical trials and has been validated in a broad range of diseases. It has eight domains: physical functioning, role limitations because of physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. These can be combined into two summary scores: physical component score and mental component score.

4.2.6 **Physical function**

Although FMS is associated with significant physical disability, leading to high medical and societal cost, there is no validated tool to measure physical disability in FMS, although there is a physical component domain within the FIQ, and SF-36 has the physical component score. Similarly, the Brief Pain Inventory has a component of physical function in its interference domains. Whether these are adequate assessment of physical function in FMS is unknown.

4.2.6.1 *Health Assessment Questionnaire*

The Health Assessment Questionnaire (HAQ) was developed for musculoskeletal diseases. It includes 20 items assessing eight domains, all of which assess physical functioning. Recently, adapted versions of the HAQ have included psychological domains so as to adopt it for assessing a condition such as FMS. Its performance as an outcome measure for FMS has not been fully assessed.

4.2.7 **Mood: depression and anxiety**

Mood disturbance, depression, and anxiety are common in FMS, and an important part of its pathophysiology. Tools used for assessing mood disturbances, depression, and anxiety can be broadly divided into two categories: screening and severity assessment.

4.2.7.1 *The Mini International Neuropsychiatric Interview*

The Mini International Neuropsychiatric Interview (MINI) is a structured diagnostic interview, which is a validated screening tool for an array of psychiatric diagnoses. It has been applied in clinical trials of FMS to exclude patients with certain psychiatric diagnoses. It is probably too extensive for use in routine clinical settings.

4.2.7.2 *Hospital Anxiety and Depression Scale*

The Hospital Anxiety and Depression Scale (HADS) is a self-reported screening questionnaire for assessing depression and anxiety. It consists of 14 questions: seven for anxiety and seven for depression. Originally developed for use in hospital medical outpatient clinics, it has been extensively used in the primary care setting. It is a useful screening tool but is insufficiently sensitive to measure change.

4.2.7.3 *The Beck Depression Inventory II*

The Beck Depression Inventory (BDI) II is extensively used in psychiatry to assess the severity of depression. It is a 21-item questionnaire, which has been extensively validated for many medical and psychiatric conditions. Although it is not a screening or diagnostic tool, it assesses the severity of depression and allows quantification of change over time. Scores of ≤9 indicate a patient is not depressed.

4.2.7.4 *Hamilton Depression Rating Scale*

The Hamilton Depression Rating Scale is a 21-item questionnaire, which is used extensively in the research of depression. The questionnaire is completed by an assessor rating the severity

of symptoms associated with depression, including low mood, insomnia, agitation, anxiety, and weight loss. It has been used in a small number of trials in FM.

4.2.7.5 *State-Trait Anxiety Inventory*

The State-Trait Anxiety Inventory (STAI) is a self-reported questionnaire with two 20-item scales for measuring state-related and trait-related anxiety. The STAI possesses strong psychometric properties for assessing changes in anxiety, but it has not been validated in FMS.

4.2.8 **Cognition**

Many patients with FMS complain of cognitive symptoms. They often report poor memory and less efficiency in processing information and performing well in demanding jobs, and find complex mental tasks to be very tiring. In the past, there was often controversy on whether the perceived cognitive problems could be demonstrated with objective testing; however, recent evidence showed that objective cognitive deficits could be demonstrated in patients with FMS. Interestingly, the cognitive impairment in patients with FMS may be different from other conditions, including chronic fatigue syndrome.

Currently, the techniques needed to objectively measure changes in cognitive function are not practical in a clinical setting. Therefore, clinical evaluation of cognitive function in FMS must rely on patient self-report. Currently, there are no validated measures for assessing cognitive function in FMS.

4.2.9 **Patient global assessment of disease**

Patient global assessment of disease activity is commonly used in clinical trials of many diseases. In clinical trials of FMS, Patient Global Impression of Change, measured on an 11-point scale, has been used extensively. It is sensitive to change. However, as a measurement of change, it is more useful for clinical trials than routine practice where measures of disease activity/status are more helpful.

4.2.10 **Catastrophizing and coping strategy**

Catastrophizing is an attributional behaviour in which pain is characterized as awful, horrible, and unbearable. Catastrophizing appears to play a substantial role in the development of pain chronicity. It predicts the onset of a chronic pain condition from an acute painful event. Catastrophizing was once thought to be a symptom of depression but is now recognized as an independent factor that is only partially associated with depression.

The Coping Strategies Questionnaire (CSQ) was first developed as a measure of the strategies utilized by patients to cope with chronic pain and as a measure of the perceived efficacy of those strategies. The CSQ assesses the use of six cognitive coping strategies (diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying or hoping, and catastrophizing) and one behavioural coping strategy (increasing behavioural activity). Each strategy subscale is composed of six items, and patients are asked to rate the frequency with which they use each strategy on a 7-point scale.

4.3 **Objective tools**

An area of intensive research is to develop objective tools for the diagnosis and assessment of FMS. Among these, the most promising is fMRI and polysomnography. Currently, they are used solely in research; because of cost and feasibility, they are not applicable in routine clinical settings.

4.4 Assessments in routine clinical practice

FMS is not a homogeneous condition. Recent research suggests there may be three subgroups according to symptom profile. The first subgroup has patients with moderate levels of anxiety, depression, and catastrophizing, and poor pain control, but with the highest pain thresholds and low tenderness. In the second subgroup, patients are those with high levels of anxiety, depression, and catastrophizing, and low pain control and considerable tenderness, whereas in the third subgroup patients have low levels of anxiety, depression, and catastrophizing, and good pain control, but with very low pain thresholds and the most tenderness. These subgroups of patients may be expected to respond to different management approaches. Given that these patients may need a different approach to treatment, assessing symptoms pertinent to these patient subgroups is important. The key assessments should include pain severity, tenderness, a screening tool for depression such as HADS, and a coping strategy such as CSQ.

4.5 Summary

A large number of instruments have been used in the assessment of FMS. Some of them have been validated in research in FMS, but there are still significant instruments that are lacking such as an appropriate tool for assessing cognition. For clinical practice, establishing a core set of assessment will be helpful, but they need to be feasible and validated in the routine practice setting.

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Chapter 5

Management of fibromyalgia syndrome

Key points

- The major objective in the management of fibromyalgia syndrome (FMS) is to empower patients to regain control over their life, by having a positive attitude and the ability to cope with the condition.
- Evidence-based guidelines have been published (American Pain Society, European League Against Rheumatism recommendations, German and Canadian Pain Society/Canadian Rheumatology Association) to guide best practice.
- A combination of, non-pharmacological and pharmacological therapies is usually needed to achieve this goal.
- New therapies for FMS are emerging, offering hope for better treatment in the future. Although these treatments are not curative, they are important adjuvants helping patients to cope with pain and improve their quality of life.

5.1 Introduction

One common misconception among the medical profession is that no effective treatment exists for FMS. Whilst it is true that no universal panacea or curative treatment exists, randomized controlled trials have demonstrated benefits of several non-pharmacological and pharmacological therapies. There are four national/international guidelines on the management of FMS: European League Against Rheumatism (EULAR) in 2006, American Pain Society (APS) in 2005, Association of the Scientific Medical Societies in Germany in 2008, and Canadian Pain Society/Canadian Rheumatology Association in 2012. Currently, EULAR is working on revising its recommendations. All these guidelines were based on systematic reviews. Although there were methodological differences in assessing the strength of evidence, they recommended similar treatments.

In order to improve the outcome of FMS, the medical profession must acknowledge the problem. The healthcare burden of FMS is undeniable. The epidemiological study in the United Kingdom showed that, in the 8 years preceding the diagnosis of FMS, the healthcare utilization for these patients was high and gradually increasing. Therefore, ignoring the problem is expensive. Since healthcare utilization decreased following the diagnosis of FMS, it provided strong evidence that constructive diagnosis and management were cost-effective. The Canadian Pain Society/Canadian Rheumatology Association guidelines emphasized this, stating that 'FM is a positive clinical diagnosis, not a diagnosis of exclusion, and not requiring specialist confirmation.' Furthermore, 'Ideal care is in the primary care setting, incorporating nonpharmacologic and pharmacologic strategies in a multimodal approach with active patient participation. The treatment objective should be reduction of symptoms, but also improved function using a patient-tailored treatment approach that is symptom-based.'

5.2 General approach to the management of fibromyalgia syndrome

Management of FMS requires a holistic approach. The diverse symptom profile compounds the individuality of each patient and demands an individualistic approach to management, rather than a 'one size fits all' attitude. FMS is not a homogeneous condition. In Chapter 4 subgroups of FMS were described. These subgroups of patients would therefore be expected to respond to different management approaches.

Hence, the management strategy must be tailor-made according to the primary symptoms of concern to that particular patient, bearing in mind co-morbidities, such as depression, and the range of treatments that have been shown to be effective. In patients with pre-existing or clinically suspected depression, potential suicide risk must be assessed. If considered at risk of suicide, urgent psychiatric referral is needed. If the patient is not at risk, they might still benefit from psychiatric referral, especially if the patient has significant current depression which is not responding to treatment.

Patient education is vital in chronic medical conditions but is even more important in FMS, as anxiety and frustration are common at the time of diagnosis. For many patients, understanding the cause and prognosis of FMS helps them to develop a coping strategy. Many charities, such as Arthritis Research UK, produce patient information sheets which can help patients to understand their condition. A vital aspect of management is to empower patients to self-efficacy. Since FMS is a chronic condition without a cure, a management plan with realistic goals should be developed jointly with patients. Patients need to understand the current treatments do not completely resolve/cure FMS. Pain may be reduced, but it is unlikely that it will remit completely. For most patients, a multimodal/multicomponent treatment strategy is needed. In most cases, a combination of non-pharmacological and pharmacological treatments is necessary. Guidelines often recommend non-pharmacological treatments should be used first. However, it is important to provide patients with advice on how to manage disease flares/worsening. In these instances, pharmacological therapy, such as analgesia, is useful. Giving patients a plan on how to manage disease flares enhances self-efficacy.

5.3 Non-pharmacological treatments

A number of non-pharmacological interventions have been examined in randomized controlled trials in FMS. These include exercise, cognitive behavioural therapy, homeopathy, physiotherapy, acupuncture, magnetism, dietary alterations, and laser therapy, among others.

5.3.1 Graded exercise

Exercise is beneficial and recommended by all guidelines, but it needs to be tailored to the individual patient's physical level. Although pain levels may increase initially, physical function, quality of life, sleep, and fatigue improve with sustained exercise. Patients should be made aware of this, so as to alleviate a common concern that exercise could worsen their condition. It is often helpful to advise patients to gradually build up the quantity of exercise.

The volume of literature supporting graded exercise in FMS is substantial. A number of systematic reviews have been published; all of them concluded that exercise is beneficial in FMS. It should be noted that exercise rarely improves pain, and this can, in fact, be worsened at first. However, physical function, tender point count, aerobic performance, and global well-being all improve with exercise. Research has shown that patients with FMS are equally able to carry out exercise as healthy people, but it needs to be tailored according to each individual. Adherence to an exercise programme is important to long-term success.

Some patients find heated pool-based exercise or hydrotherapy particularly helpful. Buoyancy reduces pressure-load onto the muscles, and the heated water provides relaxation. Pain relief may only be temporary, but treatment can be maintained long-term without any safety concerns. Treatment improves pain and function, and reduces tender point count, although the availability of a hydrotherapy pool and cost are limiting factors.

Many forms of exercise have been assessed in FMS such as aerobic and strengthening exercises; however, there is insufficient evidence to suggest any specific form of exercise is better than others.

5.3.2 **Cognitive behavioural therapy**

Cognitive behavioural therapy is a psychology-based therapy. It can improve pain and function in some individuals, either as sole therapy or in combination with exercise. It may be particularly beneficial, if provided early after diagnosis, to help patients to self-manage symptoms of FMS by developing effective coping strategies. Cognitive behavioural therapy may help to improve their long-term prognosis by providing more realistic and positive health beliefs.

5.3.3 **Warm water (balneotherapy, hydrotherapy, and spa)**

Warm water relieves pain and improves sleep and fatigue. Whilst the effects may be short-lived once treatment ceases, the risk of side effects is small. Many patients find that taking a warm water bath in the evening reduces pain and improves sleep quality.

5.3.4 **Massage**

Both American and German guidelines recommended massage therapy. Although some studies suggested massage therapy reduced pain, these were not high-quality studies, and evidence for sustained benefit remained weak. Nevertheless, the risk of side effect was low.

5.3.5 **Other therapies**

A range of dietary interventions have been studied in FMS. There is limited evidence on their effectiveness. Complementary therapies, including homeopathic remedies and acupuncture, have also been reported in the literature, but the quality of studies was poor and the results conflicting. No firm conclusion and recommendation could be made regarding these therapies. Recently, meditation, such as mindfulness therapy, has been examined in FMS. Whilst there are suggestions of benefit, more studies will be needed to evaluate its efficacy and safety.

5.4 **Pharmacological treatments**

Until recently, there was no licensed treatment for FMS. However, a number of pharmacological interventions have been shown to be efficacious in randomized controlled trials. In 2007, pregabalin was the first drug approved by the Food and Drug Administration for the treatment of FMS in the United States. Subsequently, duloxetine and milnacipran have received approval by the Food and Drug Administration.

Pharmacological treatment can be useful in combination with non-pharmacological interventions. However, not all are effective. NSAIDs are commonly prescribed for FMS to reduce pain. In clinical trials, NSAIDs appeared ineffective. NSAIDs are not recommended for treatment of FMS, unless there are concomitant conditions such as osteoarthritis.

Intolerance to medications is a well-documented problem in patients with FMS. The frequency of side effects to analgesics, NSAIDs, and tricyclic antidepressants is higher when compared with patients with low back pain and rheumatoid arthritis. The precise cause is unknown.

The hypothesis included confusion with symptoms of FMS, 'over-interpretation of sensory experiences', and central sensitization.

5.4.1 **Analgesics**

Tramadol is a weak opioid analgesic that improves pain and function in FMS. It is a centrally acting analgesic, which inhibits noradrenaline and serotonin reuptake, whilst also being an agonist for the μ-opioid receptor. Most commonly reported adverse events include nausea, somnolence, constipation, and dizziness.

Other systemic analgesics have been used in short-term studies, including lidocaine, ketamine, and morphine. There is doubt over their efficacy for treating a chronic condition such as FMS. Topical analgesics, such as lidocaine and capsaicin, are not of benefit in this condition.

5.4.2 **Antidepressants**

Antidepressants are commonly prescribed for FMS. The effects of tricyclic antidepressants, SSRIs, dual reuptake inhibitors, monoamine oxidase inhibitors, and serotonin antagonists in FMS have all been studied in randomized controlled trials.

5.4.2.1 *Tricyclic antidepressants*

Tricyclic antidepressants, such as amitriptyline, are used commonly in the management of patients with FMS. They inhibit serotonin and noradrenaline reuptake but also affect glutaminergic neurotransmission by acting on histamine, acetylcholine, and NMDA channels. Randomized controlled trials of tricyclic antidepressants, amitriptyline, and cyclobenzaprine in FMS showed that they are effective in reducing pain and improving sleep and fatigue. The beneficial effect is independent of their action on mood, as the doses prescribed are much lower than those that were used for depression. Furthermore, the correlation between improvement in mood and pain is, at best, moderate. However, the tolerability of tricyclic antidepressants is poor. Adverse effects resulting in withdrawal of treatment are common, which include somnolence, dry mouth, gastrointestinal symptoms, and neuropsychiatric disturbances. Tolerability can be improved by starting at very low doses, such as 10 mg of amitriptyline, and slowly escalating the dose, as well as giving the dose a few hours before bedtime.

5.4.2.2 *Selective serotonin reuptake inhibitors*

In general, SSRIs have fewer side effects and are better tolerated than tricyclic antidepressants. Consequently, they are often used in FMS. The SSRIs fluoxetine, citalopram, and paroxetine have each been evaluated in randomized, placebo-controlled trials, but results are mixed. In two studies, fluoxetine improved symptoms of FMS, including pain, function, fatigue, and depression. In general, the results of studies of SSRIs in FMS have paralleled the experience in other chronic pain conditions. The newer, 'highly selective' SSRIs, such as citalopram, seem to be less efficacious than the older SSRIs, which have some noradrenergic activity at higher doses.

5.4.2.3 *Serotonin and noradrenaline reuptake inhibitors*

Since tricyclic antidepressants and high doses of certain SSRIs, such as fluoxetine, inhibit both the reuptake of serotonin and noradrenaline and seem more effective than highly selective serotonin reuptake inhibitors, it led some researchers to hypothesize that dual reuptake inhibitors may be more beneficial in FMS. Although dual reuptake inhibitors lack anticholinergic effects, they may have better tolerability and side effect profile than tricyclic antidepressants.

Clinical trials have suggested that the dual reuptake inhibitor venlafaxine is a pain modulator in neuropathic pain, migraine, and tension headaches. An open-label study of venlafaxine in

patients with FMS reported improvement in pain, function, pain threshold, fatigue, and quality of life.

Randomized controlled trials of two new dual reuptake inhibitors milnacipran and duloxetine have shown that both are efficacious in the treatment of FMS.

In a placebo-controlled trial of milnacipran, 125 patients with ACR criteria-defined FMS were randomized to receive either placebo or milnacipran 200 mg daily. The dose was gradually escalated over 4 weeks to the target dose. The preliminary endpoint was changed in global pain score at week 12. At the end of the study, pain intensity was reduced by 40%, compared with 25% in the placebo-treated patients. A 50% or more reduction in pain intensity was reported by 37% of the milnacipran-treated patients, compared with 14% in those receiving placebo. Over 70% of patients reported an overall improvement in symptoms, compared with only 38% in the placebo group. Anxiety and depression improved by over 40% in the milnacipran-treated patients. Fatigue improved by over 20% and stiffness by over 30%. Physical function and quality of life also improved with treatment. Improvement in pain was independent of the effect on mood. The most frequently reported adverse event in milnacipran-treated patients was nausea. Other common side effects include abdominal pain, headache, dizziness, and palpitations.

The serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine is a licensed treatment for depression and diabetic neuropathic pain. The effect of duloxetine in FMS was examined in a randomized controlled trial in which 207 patients were assigned to receive duloxetine 60 mg twice per day or placebo for 12 weeks. At the end of the trial, patients treated with duloxetine had greater reduction of Brief Pain Inventory average pain severity score than placebo-treated patients (−2 versus −1 on a 0–10 scale), which was statistically significant. Duloxetine-treated patients also had statistically significant superior improvements in the number of tender points, stiffness, physical function, depression, and health-related quality of life than placebo-treated patients. Whether the patient suffered from major depressive disorder at baseline did not relate to improvement in symptoms and pain severity of FMS. Side effects include nausea, headaches, insomnia, constipation, and somnolence.

5.4.3 **Anti-epileptics**

Anti-epileptic drugs, such as gabapentin and pregabalin, modulate pain perception by increasing inhibitory neurotransmission and blocking calcium and/or sodium channels. Their benefit has been demonstrated in chronic pain conditions such as post-herpetic neuralgia and painful diabetic neuropathy.

Pregabalin, an analogue of GABA and an alpha-2-delta agonist, was the first medication to be licensed for the treatment of FMS in the United States. In a placebo-controlled trial, 529 patients with FMS were randomized to receive either placebo, or 150, 300, or 450 mg/day of pregabalin. The dose was escalated to the target dose over 2 weeks. Patients receiving pregabalin 450 mg/day had statistically significantly greater reduction in the severity of pain than placebo-treated patients. There were also significant improvements in sleep quality, fatigue, and global measures of change. The commonest side effects were dizziness, somnolence, weight gain, and dry mouth. Pregabalin is approved in the United States at doses of either 300 or 450 mg/day.

5.4.4 **Sleep modifiers**

Since poor sleep quality is common in FMS, sedatives/hypnotics are widely prescribed for patients with FMS. Hypnotics, such as zolpidem, act on benzodiazepine receptors that have been shown to improve sleep and fatigue in patients with FMS. However, they did not improve pain; hence, they should be used in combination with other treatments.

The effect of sodium oxybate in FMS was examined in a randomized controlled trial. Sodium oxybate is a precursor of GABA, which increases slow-wave sleep and growth hormone levels.

It is licensed for the treatment of narcolepsy. In randomized controlled trials, improvement in sleep quality was accompanied by reduction in pain and fatigue. However, the prescription of sodium oxybate is highly controlled and regulated because of a high risk of abuse. It is not recommended for the treatment of FMS.

5.5 Empowering patients to self-management

In order to improve the prognosis of FMS and reduce its burden on patients, their family, healthcare funders, and society, it is vital that the condition is recognized and better understood by patients and clinicians. The major goal is to enable patients to regain control over their life, by having a positive attitude and coping better with the condition. Understanding each patient's needs and developing a treatment regimen, using a combination of non-pharmacological and pharmacological therapies, based on the individual's key clinical manifestations and circumstances are critical to achieving this therapeutic objective. Although management options have been limited in the past, new therapies for FMS are emerging, offering hope for better treatment in the future. Whilst these treatments are not curative, they are important adjuvants, helping patients to cope better with pain and improve their quality of life.

Suggested reading

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Chapter 6

Quick practical guides

The purpose of this chapter is to provide quick summaries and tips to help clinicians with the diagnosis and management of patients with FMS in daily practice.

6.1 Diagnosing fibromyalgia syndrome

6.1.1 Useful practical hints for diagnosing fibromyalgia syndrome

6.1.1.1 *History*

- Ask about site, duration, onset, and severity of pain.
- Ask patients whether they feel tired all the time.
- Ask patients whether they sleep well and whether they feel refreshed in the morning.
- Ask patients whether they feel depressed or anxious, or feel pressurized/stressed at home and at work. In patients with depression, ask whether they have any suicidal thoughts. The presence of the latter will need urgent psychiatric assessment.
- Ask patients whether they have any problem with memory or difficulties with concentration, problem-solving, and learning new tasks.
- Ask about the impact of illness on daily life, work, and social relationships.
- Remember to ask the 'red flag' symptoms: unexplained weight changes, fever, and snoring.

6.1.1.2 *Examination*

- Conduct general medical examination, and assess the number of FM tender points (Figure. 6.1 and Table 6.1).
- Remember the 'red flag' signs: joint swelling, muscle weakness, abnormal gait, skin rashes, delayed tendon reflexes, lymphadenopathy, and focal neurological signs.

6.1.2 Tender point count

1. The thumb pad of the examiner's dominant hand is used to apply pressure to the evaluation sites during the tender point examination.
2. First, the evaluation site should be located visually. Then, the evaluation site should be pressed perpendicularly for 4 seconds.
3. The site should be pressed only once to avoid sensitization.
4. Four kilograms of pressure should be applied to the site, and it is enough force to blanch the examiner's nail bed.
5. The patient should sit on the examination table for evaluation of the first 14 sites. They should lie on their sides, contralateral to the site to be tested, for the greater trochanters, and they should lie on their backs for the knees.
6. The patient should respond with a 'yes' or 'no' if they have any pain at the site being examined.

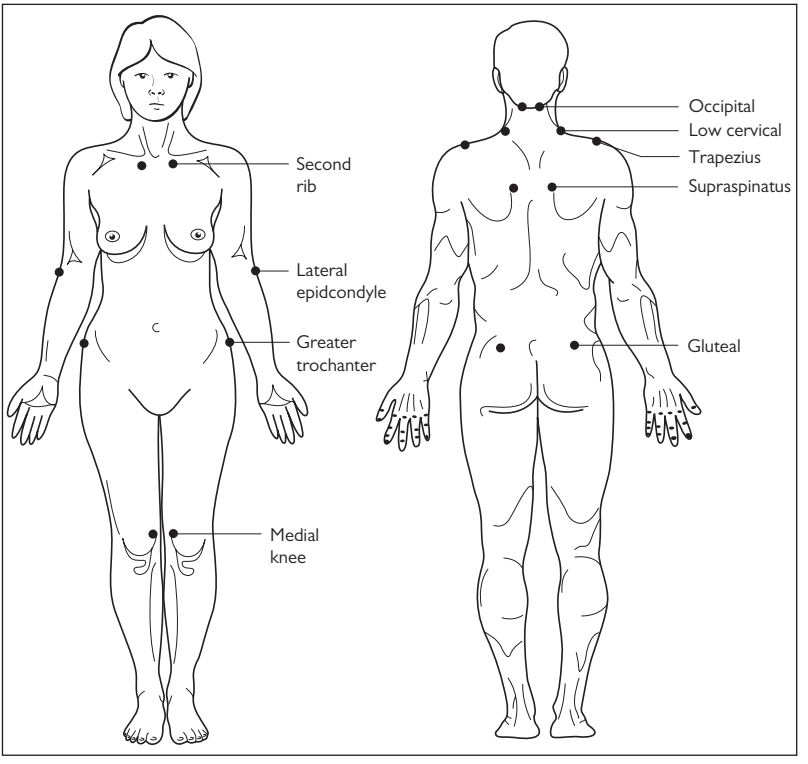

Figure 6.1 American College of Rheumatology classification criteria for fibromyalgia: tender point sites. Reproduced with permission from Wolfe F, Smythe HA, Yunus MB, *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum*, 1990; **33**: 160–72.

6.1.3 **Widespread Pain Index**

Note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? The score will be between 0 and 19:

- Shoulder girdle (left and right)
- Upper arm (left and right)
- Lower arm (left and right)
- Hip (buttock, trochanter) (left and right)
- Upper leg (left and right)
- Lower leg (left and right)
- Jaw (left and right)
- Chest
- Abdomen
- Upper back

- Lower back
- Neck.

Table 6.1 American College of Rheumatology classification criteria for fibromyalgia: tender point sites	
Bilateral sites	**Anatomical location**
Occiput	At the nuchal ridge, laterally one-thumb width to the insertion of the suboccipital muscle to the occiput
Low cervical	At the fifth through to seventh intertransverse spaces of the cervical spine
Supraspinatus	At the craniomedial border of the scapula at the origin of the supraspinatus
Trapezius	At the upper border of the shoulder in the trapezius muscle, midway from the neck to the shoulder joint
Second rib	In the pectoral muscle at the second costochondral junctions
Lateral epicondyle	Approximately three-finger breadths (2 cm) below the lateral epicondyle
Gluteal	In the upper outer quadrant of the gluteus medius
Greater trochanter	Just posterior to the prominence of the greater trochanter at the piriformis insertion
Medial knee	At the medial fat pad, proximal to the joint line

Reproduced with permission from Wolfe F, Smythe HA, Yunus MB, *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum*, 1990; **33**: 160–72.

6.1.4 **Symptom Severity Scale**

The SSS score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

For each of fatigue, waking unrefreshed, and cognitive symptoms, indicate the level of severity over the past week using the following scale:

- 0 = no problem
- 1 = slight or mild problems, generally mild or intermittent
- 2 = moderate, considerable problems, often present and/or at a moderate level
- 3 = severe: pervasive, continuous, life-disturbing problems.

Considering somatic symptoms* in general, indicate whether the patient has:

- 0 = no symptoms
- 1 = few symptoms
- 2 = a moderate number of symptoms
- 3 = a great deal of symptoms.

* Somatic symptoms that might be considered include: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps

in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

6.1.5 **American College of Rheumatology 2010 preliminary diagnostic criteria**

A patient satisfies the diagnostic criteria for FM if the following three conditions are met: WPI ≥7 and SSS score ≥5, or WPI between 3 and 6 and SSS score ≥9; third, the patient does not have a disorder that would otherwise explain the pain.

6.2 **Assessment of pain**

6.2.1 **Pain drawing**

Instructions: use a pencil or pen to mark darkly on the body diagrams (Figure 6.2) showing the locations of your pain during the last week.

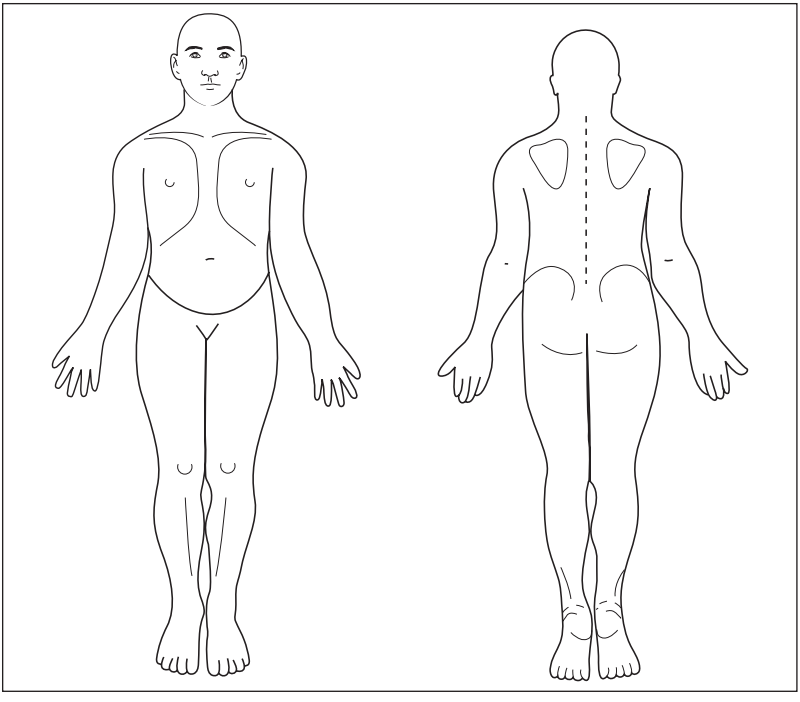

Figure 6.2 Mannequin for pain drawing.

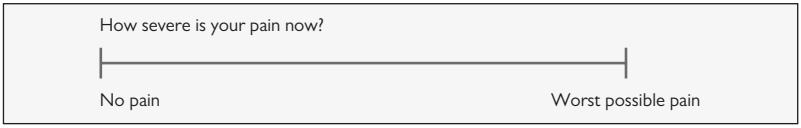

Figure 6.3 Visual analogue scale of pain.
Reprinted from *The Lancet*, Huskisson EC (1974). Measurement of pain. *The Lancet*, **304**: 1127–31, Copyright (1974), with permission of Elsevier.

6.2.2 **Visual analogue scale of pain**

For the VAS of pain, see Figure 6.3.

6.3 **Fibromyalgia Impact Questionnaire**

For the FIQ, see Figure 6.4.

6.4 **Quick guide to management**

6.4.1 **Quick tips**

Many doctors feel diffident in managing patients with FMS. The reasons include a lack of understanding of the underlying pathophysiology, the plethora of symptoms, and a misconception that nothing can be done. This often results in a negative consultation, which is frustrating for both the patient and doctor. Here are a few key tips.

1. Be a good listener.
2. Assess the patient for severity of pain, tenderness, depression and anxiety, and coping, if possible using self-report forms and questionnaires.
3. Do not assume that depression is the basis of FMS in all patients. In fact, not all patients are depressed. It is easy to confuse psychosocial stress with depression.
4. In patients with pre-existing or HADS-positive or clinically suspected moderate to severe depression, assess for suicide risk. If considered at risk, an urgent psychiatric referral is needed. If the patient is not at risk, they should still benefit from psychiatric referral, especially if the patient accepts he/she has significant depression or knows his/her mood has deteriorated.
5. Although pain is a subjective symptom and cannot be seen, research has shown that these patients are not malingerers. When they complain of pain, that is what their brain is telling them. It is important not to cast doubt on their complaint.
6. Be constructive, and explain the nature, prognosis, and treatments available to the patient. Reassure them, and discuss the treatment strategy.
7. Non-pharmacological interventions are very important. Highlight what patients can do for themselves: warm water bath and graded exercise. Warn patients that pain may worsen transiently when starting exercise but that it should be persevered. Consider cognitive behavioural therapy, relaxation, rehabilitation, physiotherapy, and psychological support which may be used, depending on the needs of the individual patient.
8. Pharmacological treatments, as recommended by the EULAR recommendations, may be a useful adjunct and should be considered. Choice will depend on clinical manifestations.

Fibromyalgia Impact Questionnaire (FIQ)

Last name: First name: Age: Todays date:

Duration of FM symptoms (years): Years since diagnosis of FM:

Directions: For questions 1 through 11, please check the number that best describes how you did overall for the *past week*. If you don't normally do something that is asked, place an 'X' in the 'Not Applicable' box.

Were you able to:	Always	Most	Occasionally	Never	Not Applicable
1. Do shopping?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Do laundry with a washer and dryer?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Prepare meals?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Wash dishes/cooking utensils by hand?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Vacuum a rug?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Make beds?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Walk several blocks?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Visit friends or relatives?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Do yard work?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Drive a car?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Climb stairs?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Sub-total scores (*for internal use only*)	☐	☐	☐	☐	☐
Total score (*for internal use only*)	☐				

12. Of the 7 days in the past week, how many days did you feel good? Score ☐

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

13. How many days last week did you miss work, including housework, because of fibromyalgia? Score ☐

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Directions: For the remaining items, mark the point on the line that best indicates how you felt overall for the past week.

14. When you worked how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework? (for internal use only)

No problem with work ——— Great difficulty with work ☐ Score

15. How bad has your pain been?

No pain ——— Very severe pain ☐ Score

16. How tired have you been?

No tiredness ——— Very tired ☐ Score

17. How have you felt when you get up in the morning?

Awoke well rested ——— Awoke very tired ☐ Score

18. How bad has your stiffness been?

No stiffness ——— Very stiff ☐ Score

19. How nervous or anxious have you felt?

Not anxious ——— Very anxious ☐ Score

20. How depressed or blue have you felt?

Not depressed ——— Very depressed ☐ Score

☐ Sub-total

☐ FIQ total

Figure 6.4 Fibromyalgia Impact Questionnaire.

9. 'Start low and go slow' is the motto for using medications. Patients with FMS are often very sensitive to side effects from treatment. In many instances, it may be difficult to separate symptoms of FMS from the side effects of treatment. There are also studies which show that FM patients are more sensitive to treatment side effects. So start on the lowest dose, and gradually titrate it upwards.
10. Explain to the patients that the maximum benefit for pain modification treatment, such as the antidepressants, may take several weeks to exert its maximum effect. Many patients think such treatments are painkillers and expect them to work immediately. If this is not explained, they often give up treatment because they do not respond after a few days.
11. It is vital patients have a realistic expectation from medications. They are not a cure for FMS. On their own, they are not the whole answer. Patients must not ignore the non-pharmacological interventions.
12. Do NOT advise patients to avoid all activities and rest all the time.
13. Work with patients to develop treatment goals and a self-management strategy.

6.5 **A practical self-help guide for patients**

Here are some practical tips that many patients find helpful.

6.5.1 **Patient education**

6.5.1.1 *Leaflets*

- FM information pack from Fibromyalgia Association UK.
- Arthritis Research UK patient information leaflet on FM.

6.5.2 **Patient support groups**

- Fibromyalgia Association UK.

6.5.3 **Useful websites**

- http://www.fibromyalgia-associationuk.org
- http://www.arthritisresearchuk.org

6.5.4 **Warm water bath**

Many patients find warm water soothing and relaxing. Having warm baths in the morning and evening often helps to start the day and, for many patients, to sleep better at night.

6.5.5 **Exercise**

Do not be afraid of exercise. Many patients avoid exercise, because their muscles are more painful afterwards. Aching after exercise is normal. Exercise does not cause more damage in FMS. Start gradually, and tend to build up the amount of exercise you do gradually. If you have not done exercise for some time, your muscles may ache more. Get advice from your doctor, physiotherapists, or an advisor from a fitness centre to give you advice on how to build up your exercise.

Try exercise in the evening, and take a warm bath afterwards. Many patients find it also helps them to sleep better.

6.5.6 **Sleep**

If the quality of sleep is poor, you do not feel refreshed in the morning, and your partner complains about your snoring, you should tell your doctor. Your doctor may need to refer you to a specialist to see whether you have a specific illness 'sleep apnoea syndrome'.

6.5.7 **Mood**

Depression, anxiety, and stress can all aggravate FMS. Some patients suffer from depression for many years before they develop FMS. They often notice that depression and anxiety make pain, fatigue, and sleep worse. It is important to discuss this with your doctor, especially if it is very bad; you may need additional help from a psychiatrist and psychologist. Although depression is not the main cause of FMS, it may be difficult to reduce pain without improving the mood in patients who have severe depression.

6.5.8 **Dealing with stress**

Stress can worsen FMS. Identify areas of life which are stressful; taking measures to reduce stress at work and in the family can be very helpful. Your doctor may provide a letter to explain the nature of FM to your employer. It is good for patients with FMS to work. It improves the overall quality of life. The key is to find ways to adapt and reduce excessive stress. Cognitive behavioural therapy can be helpful in developing realistic achievable goal.

6.5.9 **Living and coping with fibromyalgia syndrome**

Like many patients with chronic medical illnesses, finding ways to cope is very important. Many patients with FMS feel frustrated and pessimistic. It is important to accept that FMS is a chronic illness; there is no universal panacea. However, treatment can reduce the severity of symptoms, allowing patients to regain control over their life.

6.6 **When to investigate**

It is important not to overinvestigate. Incidental non-clinical significant findings can cause unnecessary anxiety.

Here are a few suggestions on when to investigate:

1. The presence of objective physical signs
2. New symptoms when all other aspects of FMS are stable
3. Unexpected significant weight loss or gain
4. Fever
5. When a symptom is very persistent and worsening.

6.7 **Summary**

It is important to diagnose and manage FMS positively. The key word is to regain control both for the doctor and the patient.

Chapter 7

Case studies

7.1 Case 1: a typical case of fibromyalgia syndrome

A 50-year-old environmental manager has developed severe pain over the right costochondral area over the last 18 months. The pain is present especially during the daytime. She has no nocturnal symptoms and has no problem in the morning. She finds that stress aggravates her problem. In addition, she also has pain affecting her arms, legs, back, and neck. These tend to be mechanical, worsened by movement, and relieved by rest. She has early morning stiffness that lasts all day. Her joints feel swollen all the time. She admits to sleeping poorly and has occasional paraesthesiae and numbness in her hands. Her weight has been steady. Her only current medication is hormone replacement therapy (HRT), which she takes to control mood swings.

On examination, her joints appeared normal. There was no detectable synovitis. She had multiple fibromyalgic tender points.

7.1.1 Investigations

FBC, biochemistry, ESR, and C-reactive protein (CRP) were normal. Rheumatoid factor (RF) was negative. Anti-nuclear antibody was present at a titre of 1:20. Other auto-antibody tests were negative. Thyroid function tests were normal.

7.1.2 Learning points

- Many patients with FM complain of joints feeling swollen and have prolonged early morning stiffness. This may be confused with inflammatory arthritis.
- Non-restorative sleep is common in FM.
- It is important to enquire about depression.
- It is important to enquire about work and family situation, and whether the patients are under any stress.
- The role of investigations in FMS should be discussed.

7.2 Case 2: secondary fibromyalgia syndrome

An 18-year-old woman suffers from juvenile chronic arthritis since the age of 13. Initially, she developed a sudden onset of pain in several joints, including the ankles, knees, feet, hands, elbows, shoulders, and neck. Swelling has been noticed, particularly in the hands and elbows, with early morning stiffness lasting 1 hour. The patient also describes locking of the left elbow. The patient was previously treated with methotrexate, and her condition improved initially. Her condition worsened 3 years ago with more aches and pains in her joints. She suffers from widespread muscular pain; cramps in the legs and, to a lesser extent, in the hands, particularly at night; fatigue; non-refreshing sleep; migraine; stomach pain; numbness in the hands and feet;

and pain in the loin. She has an episode of chest pain which is not related to exertion. Past medical history includes migraine, asthma, irritable bowel syndrome, and urinary frequency.

Physical examination revealed a number of tender joints, including feet, hands, ankles, knees, wrists, elbows, and shoulders. None of the joints was swollen. FM tender points were positive (12 out of 18).

7.2.1 **Investigations**

- FBC and biochemistry: normal.
- ESR: 11 mm/hour.
- CRP: negative.

The methotrexate dose was escalated, but the patient did not respond. She complained that methotrexate made her dizzy and sick. She wanted to stop methotrexate.

7.2.2 **Learning points**

- Secondary FMS is not uncommon in patients with inflammatory arthritis.
- It should be suspected in patients with a lot of tenderness or tender joints but no synovitis and no acute phase response.
- Patients with FMS are more likely to complain of side effects from medications.
- These 'side effects' are not easily distinguishable from symptoms of FMS, causing confusion.
- Careful evaluation and discussion are needed regarding stopping what might have been an effective treatment for the inflammatory condition.

7.3 **Case 3: confusion with inflammatory arthritis**

A 34-year-old care worker for disabled people had an approximately 5-month history of pain and swelling in the small finger joints, the right elbow, and both hips and knees. She suffered from pain all the time, which was aggravated by activities such as driving or opening jars. It sometimes woke her at night. She had early morning stiffness lasting almost all day. Aside from pain, fatigue was a major problem.

The patient did not complain of skin rash, weight change, Raynaud's phenomenon, or neurological symptoms. Her past medical history included gestational diabetes, lichen sclerosis, migraine, dyspepsia, and long-standing mechanical knee pain.

The patient was taking ibuprofen 400 mg, up to six tablets per day, but she found it of limited efficacy. In contrast, felbinac gel was helpful.

On examination, the skin and nails were normal. Neither nodule nor lymph node was present. Some joints were tender, without any evidence of synovial joint swelling. Fifteen out of 18 FM tender points were present. The rest of the examination was unremarkable.

7.3.1 **Investigations**

Negative or normal ESR, CRP, blood count, RF, auto-antibodies, liver function tests, and renal function tests. Radiographs of her hands and feet were normal.

7.3.2 **Learning points**

- In some cases, differentiating FMS from viral-induced inflammatory arthritis may be difficult, as patients may complain of prolonged early morning stiffness and joint swelling.
- Whilst many patients with FMS may complain of swollen joints, objective evidence of synovitis is often absent.

7.4 Case 4: overlap with chronic fatigue syndrome

A 45-year-old writer went abroad for a holiday and developed an episode of viral illness of 2 weeks' duration, characterized by fever, malaise, sore throat, headache, and dry cough. At the time, she also experienced generalized muscle pain and fatigue. She was admitted to hospital for investigation, but no abnormality was found. Her fever settled, and her general condition improved. However, she developed pain in her hands, shoulders, hips, knees, neck, and lower back, which was constant and aggravated by physical activities. Aside from pain, fatigue was a major problem. She described attacks of severe fatigue which left her completely washed out. She had to give up work and found household chores impossible. Her mood was low because of the persistent pain.

The patient had no other complaints. Her past medical history included an episode of depression after the death of her mother. She took paracetamol for the pain, but it was ineffective.

General medical examination was normal. No lymph node was palpable. Joints were tender but not swollen. Eighteen FM tender points were present.

7.4.1 Investigations

Results of blood tests were normal.

7.4.2 Learning points

- FMS may overlap with chronic fatigue syndrome.
- Some patients complain of a viral infection before disease and may have been extensively investigated for persistent infection.

7.5 Case 5: chronic localized pain and fibromyalgia syndrome

A 63-year-old retired cleaner to our clinic presented with long-standing mechanical low back pain with periodical flares over the past 10 years. Each flare lasted 4–6 weeks. Attacks occurred approximately once every 2 months. Although, in between attacks, she experienced a dull ache in her lower back, during these flares, she found it difficult to walk. Bending, prolonged standing, and coughing all aggravated the pain. There was also a history of mechanical pain in the right knee and hip which came on after walking for 15–20 minutes. Finally, she also suffered from fairly regular attacks of pain in the neck, for which she had to consult an osteopath. Otherwise, the patient felt well in herself, but her current complaints include cataracts, paraesthesiae in the hands and feet, as well as a 'funny feeling' in the stomach with a recent onset of vomiting. Over the last year, her symptoms had got worse. It had become more diffuse throughout her body. It was present virtually all the time. She felt tired and slept poorly. Finding a good position to sleep was difficult.

Physical examination revealed reduced flexion in both knees. The right knee was particularly painful, and mild crepitus could be detected. There was tenderness over the lumbar spine, mainly over L5. There was also tenderness over the iliac crest bilaterally. Both flexion and, to a lesser extent, extension of the lumbar spine were painful. Straight leg raising was 80° on the left and 70° on the right, with negative sciatic and femoral nerve stretch tests. There were no abnormal neurological signs, and tests for carpal tunnel syndrome were negative. The cervical spine showed restricted range of motion that was painful. Again, there was no evidence of referred pain or neurological sign. Eleven out of 18 FM tender points were present.

7.5.1 **Investigations**

Results of blood tests were normal. A radiograph of her lumbar spine showed reduced disc space at L4/5 and L5/S1. Her neck X-ray showed degenerative disease with osteophytes and reduced disc space at C5/6. Her knee and hip X-rays showed mild reduction in joint space but were otherwise normal. A magnetic resonance imaging (MRI) scan of her neck and lower back only confirmed results of the plain radiograph, without any evidence of disc prolapse or nerve entrapment.

7.5.2 **Learning points**

- FMS may sometimes develop in patients with chronic localized musculoskeletal pain such as osteoarthritis, or neck or low back pain.
- It has been postulated that, in these patients, 'sensory spreading' from central sensitization may be the underlying pathophysiological process.

7.6 **Case 6: a subtype of fibromyalgia syndrome (low levels of depression and anxiety, normal cognition, tenderness)**

A 35-year-old police officer doing mainly clerical work complains of multiple joint pain, affecting mainly the neck, shoulder girdle, lower back, and legs, for 5 years. There is significant stiffness in all joints. Her symptoms tend to be aggravated by factors such as stress, cold weather, protracted walking, and climbing stairs, whereas alleviating factors are relaxing activities such as playing chess and rest and comfortable position. In spite of this, the patient usually has significant pain at night, especially turning over in bed. She sleeps poorly at night. She finds it difficult to get to sleep and often wakes up early in the morning. She never feels refreshed in the morning and is tired all the time. The low back pain is of a dull aching type, with superimposed episodes of sharp pain, and these are referred to the thighs. She sometimes has paraesthesiae in the legs, and previously in the feet, but no numbness. Walking distance is limited because of shortness of breath and joint pain as well.

She also suffered from severe neck pain, which radiated to the back of her head and triggered off severe headache. She had a long history of suffering from headache, which was investigated extensively, including repeated MRI scans, by a neurologist. No abnormality was found, and she was told that the headache was atypical migraine.

She lives with her husband and two children in a house, which has a lot of stairs. There is a lot of pressure at work, and she has noticed that the pain was worse when her stress level was high. Her line manager was neither understanding nor sympathetic. She told her that she had been taking too much sick leave and she looked well to her anyway. Although it was difficult, she has continued working.

At times, she has felt depressed and finds it difficult to cope during bad periods. However, her husband has been very supportive, and it made a lot of difference. After taking a 2-week holiday, she was feeling much better.

On examination, there was no evidence of synovitis in the peripheral joints, skin rash, or skin nodules. She has a restricted active range of motion of the cervical spine, with an approximately normal passive range of motion. She had 11 out of 18 FM tender points. Flexion of the lumbar spine was slightly reduced because of pain.

7.6.1 **Investigations**

Her blood tests and X-rays were normal. Using the HADS questionnaire, it was found that she has mild depression and anxiety.

7.6.2 **Learning points**

- A common subtype of FMS is represented by patients who have pain but only a few tender points, although sufficient in number to fulfil the ACR criteria. They often have mild depression and anxiety, but they are coping with the pain.
- Antidepressants may be particularly helpful.

7.7 **Case 7: a subtype of fibromyalgia syndrome (high level of tenderness and depression)**

A 52-year-old retired author presented with long-standing generalized pain in her joints and muscles over the past 15 years. The patient feels her symptoms started when she was attacked by robbers and was hit at the back of the head and kicked repeatedly. Recently, the pattern of pain has changed. It is now more severe, frequently severe at night. All her joints are affected, including her neck and back. She cannot do anything. The patient is in considerable pain in the evening when sitting down. Any movement tends to aggravate the pain. She cannot even hold a pen or a cup. She cannot get comfortable in bed. The pain is so severe that she cannot get to sleep. She only sleeps 2–3 hours at night. Consequently, she is completely washed out. Her appetite is poor. She has a history of suffering from depression. Her mood is very low, often tearful, and she feels she cannot cope anymore. She is stiff all day and cannot understand clearly why she seems to be in a 'fog' all the time. It is impossible for her to write, and her memory is poor. She suffers from dizziness, palpitation, and excessive swelling. She had two blackouts and was admitted to hospital through the accident and emergency department. She had extensive investigations organized by cardiologists and neurologists; an MRI scan, echocardiography, 24-hour electrocardiograms (ECGs) were all normal. She is very concerned because no cause has been found for these blackouts. Her hands and feet suffer from attacks of numbness and paraesthesiae.

There is also no history of bowel problems: dyspepsia, diarrhoea, and abdominal pain. She is currently being investigated by a urologist for frequent urination and dysuria, but her repeat urinary cultures are normal.

She is given different kinds of medicines, but they all make her sick. She gets side effects from all of them, and they are not helpful in any way. She cannot remember the names of these medications.

In the middle of the consultation, she bursts out in tears and claims she cannot cope with all these problems anymore.

Examination revealed absence of synovitis, skin rash, and lymphadenopathy. Her chest was clear, and there were no abnormal heart sounds. Neurological examination was normal. Eighteen FM tender points were present. She was tender seemingly all over. It was difficult to examine the patient, as she appeared very tense. Back and neck movements were restricted in all directions because of pain.

7.7.1 **Investigations**

FBC, biochemistry, RF, ESR, and CRP were normal or negative. Anti-nuclear antibody was present at a titre of 1/20, but anti-double-stranded DNA antibodies were absent. X-rays of the cervical spine, lumbar spine, hands, and feet revealed minor degenerative changes but no other abnormalities. A nerve conduction study was normal. A 12-lead ECG, chest X-ray, echocardiography, 24-hour ECG, and MRI scans of the brain and spine were all normal.

7.7.2 **Learning points**

- This type of FM patient is commonly seen in secondary and tertiary care. They are characterized by a high number of tender points, tenderness, high level of anxiety and depression, disturbed cognition, and loss of control or catastrophizing, defined as having a very negative and pessimistic view of their pain. They are polysymptomatic, and sympathetic symptoms are common.
- Low titres of auto-antibodies, such as anti-nuclear antibody, are found in normal individuals; on their own, they are not diagnostic for autoimmune diseases.
- Many patients with FMS gave a history of significant depression pre-dating the development of chronic widespread pain. Often these patients have a depression-driven FM. They should be referred to a psychiatric team for management.
- In patients with significant depression and expressing hopelessness, it is important to enquire about suicidal thoughts. Those patients with suicidal thoughts should be referred for an urgent psychiatric assessment.
- This patient subtype has the worst prognosis.

7.8 **Case 8: a subtype of fibromyalgia syndrome (tender, no negative psychological or cognitive factors)**

A 42-year-old manager has suffered from widespread pain in her joints and muscle for 20 years. She could not remember how it started but seemed to have suffered from it as far as she could recall. There was no specific precipitating event or aggravating or relieving factor. There is significant variation in severity from day to day. She feels tired, but she puts this down to either being very busy at work or sleeping poorly. Although she sleeps for 8 hours per night, she does not feel refreshed in the morning. The pain has got worse recently. She and her husband have noticed that even light touch can cause pain. They have become alarmed and therefore seek medical advice. Otherwise, her general health is good. Mood is normal, and there is no history of cognition problem.

Examination revealed 14 FM tender points, but general medical examination was normal. Light pressure was sufficient to elicit pain.

7.8.1 **Investigations**

FBC and biochemistry were normal. The patient completed the HADS questionnaire, which was normal.

7.8.2 **Learning points**

- This patient subtype has a good prognosis.
- Patients with significant functional impairment should be encouraged to exercise.
- Cognitive behavioural therapy may be helpful.

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